OCTOBER 1953

BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles

by

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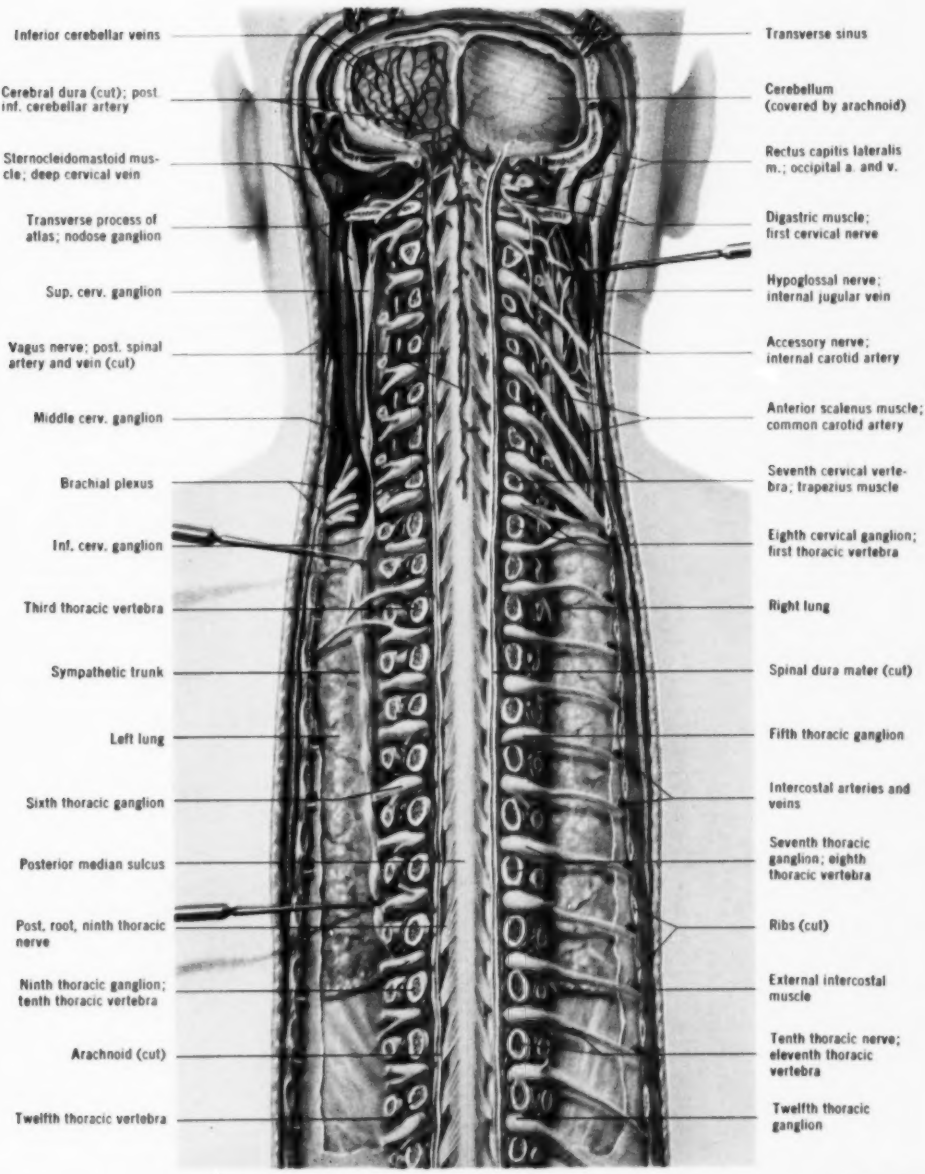
Inferior cerebellar veins
Cerebral dura (cut); post. inf. cerebellar artery
Sternocleidomastoid muscle; deep cervical vein
Transverse process of atlas; nodose ganglion
Sup. cerv. ganglion
Vagus nerve; post. spinal artery and vein (cut)
Middle cerv. ganglion
Brachial plexus
Inf. cerv. ganglion
Third thoracic vertebra
Sympathetic trunk
Left lung
Sixth thoracic ganglion
Posterior median sulcus
Post. root, ninth thoracic nerve
Ninth thoracic ganglion; tenth thoracic vertebra
Arachnoid (cut)
Twelfth thoracic vertebra
Transverse sinus
Cerebellum (covered by arachnoid)
Rectus capitis lateralis m.; occipital a. and v.
Digastric muscle; first cervical nerve
Hypoglossal nerve; internal jugular vein
Accessory nerve; internal carotid artery
Anterior scalenus muscle; common carotid artery
Seventh cervical vertebra; trapezius muscle
Eighth cervical ganglion; first thoracic vertebra
Right lung
Spinal dura mater (cut)
Fifth thoracic ganglion
Intercostal arteries and veins
Seventh thoracic ganglion; eighth thoracic vertebra
Ribs (cut)
External intercostal muscle
Tenth thoracic nerve; eleventh thoracic vertebra
Twelfth thoracic ganglion

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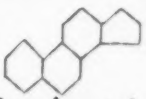
the symbol SCHERING denotes leadership in steroid hormone  research and manufacture -- including Cortogen in the most useful clinical forms. For systemic therapy, use Cortogen tablets or injection . For eye disorders use Cortogen ophthalmic suspension -- sterile . The Schering seal appears on each tablet and package -- your assurance of quality.

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*Glazebrook, A. J.: Brit. M. J., 2:1328 (Dec. 20) 1952.

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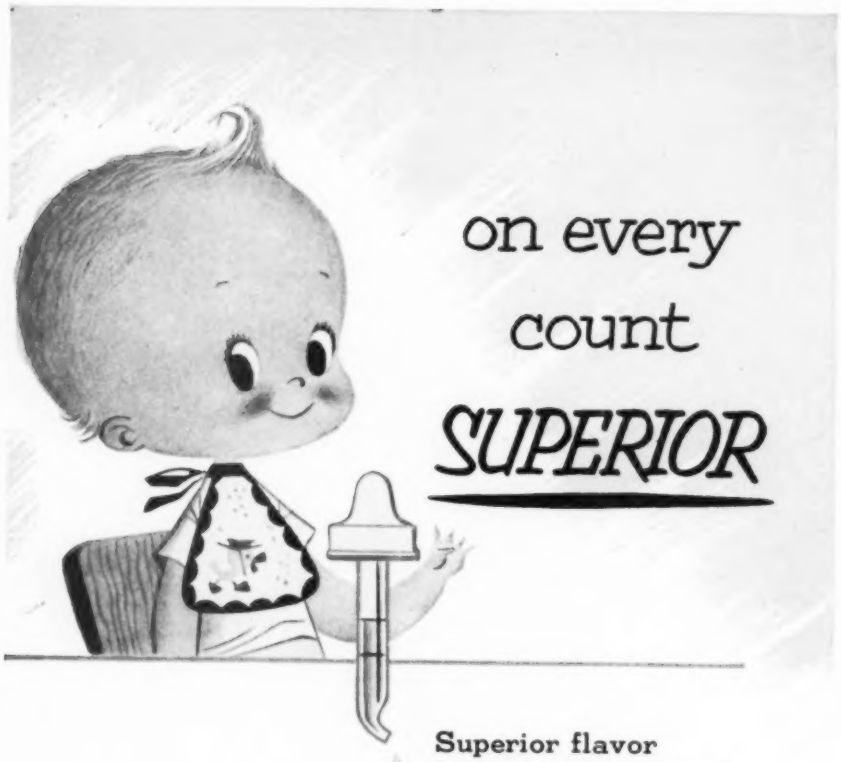

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*Annals of Internal Medicine, 37:465, 1952.

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

ROBERT L. CRAIG, *Editor*

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BULLETIN OF
THE NEW YORK ACADEMY
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VOL. 29, NO. 10 OCTOBER 1953

PHEOCHROMOCYTOMA*

GEORGE F. CAHILL

Professor of Urology, College of Physicians and Surgeons, Columbia University

PHEOCHROMOCYTOMA, a tumor of the chromaffin sympathetic nerve tissue, formerly considered to be very rare, seems to be now more frequently recognized than before, if one may judge from reports in the literature.

Recently it has been shown that these tumors produce the pressor catechols, epinephrine and norepinephrine in variable excess quantities and that these substances produce the hypertensive symptoms. Also in addition, pharmacological tests have been described, some stimulating the release of the pressor substances and others combating their effects, when they are present in excess amounts. From the use of these tests a more probable diagnosis was possible among the various hypertensives and enough tests have been performed to estimate their value. In addition, quantitative estimation of the catechols in the urine is now possible, not with too great a degree of accuracy but sufficiently accurate for a correct diagnosis. Also the more widespread use of retroperitoneal gas insufflation has definitely helped the location of the site of the tumor. Also, for this purpose aortograms and venograms have been done. Lastly,

* Presented at the 25th Graduate Fortnight of The New York Academy of Medicine, October 10, 1952.

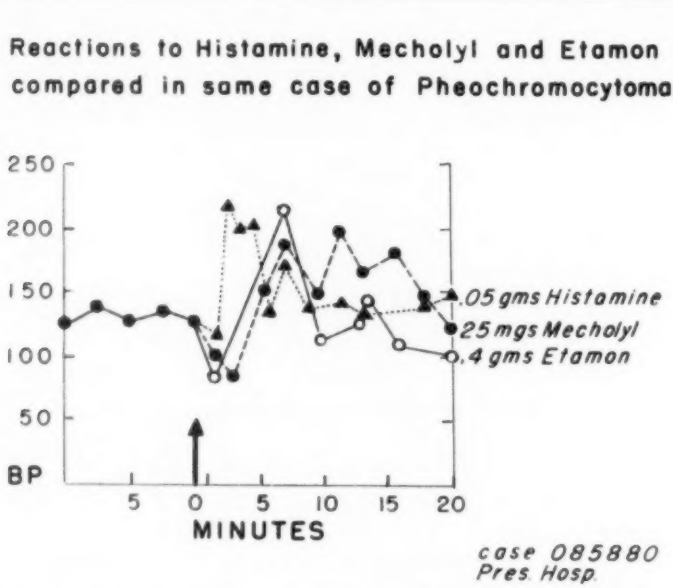

Chart 1. Blood pressure readings after injections of histamine, Mecholyl and Etamon given to the same patient at different times. From this it can be seen that histamine acts quicker and the effect is shorter.

experience with the chemical control of the symptoms has greatly improved the therapeutic operative removal.

From a survey of 139 cases in which the exact location of the tumor was stated, the occurrences were as follows: Right adrenal seventy-two, left adrenal forty-four, both adrenals thirteen, interthoracic four, intercerebral one, right aortic ganglia two, left inferior aortic ganglia, and Zuckerkandl's ganglia two. The tumor is most frequently seen in adult life, although the ages have ranged from sixteen months to eighty-two years. Only seven cases have been reported in children up to 1951. The ratio of sex occurrence was females seventy-two, males fifty-five. There is a family tendency in some cases and about 5 per cent have coincidental cutaneous neurofibromatosis, which also has a familial tendency. Of 121 cases in which race was mentioned only two occurred in Negroes. Other endocrine disorders occur with the syndrome, thyroid pathology, Addison's disease, adrenogenital syndrome and Cushing's adreno-cortical syndrome have been reported. About 16 per cent of the cases have multiple tumors, usually two, and only very rarely more. Most of the tumors are

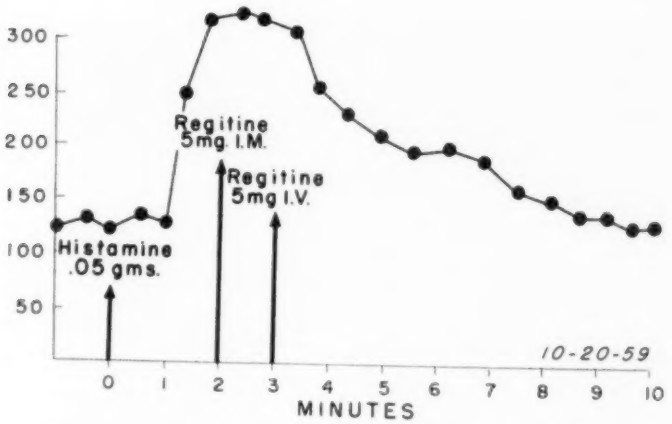

Chart 2. A case in which the reaction to a histamine injection was of such intensity that it was necessary to reverse the effect by intramuscular and intravenous injections of Regitine.

benign. Of the 8 per cent reported as malignant, some have hypertensive symptoms only at the onset, some during most of their existence and a few no hypertensive symptoms at any time.

It had been the accepted explanation that the occurrence of hypertension in these cases was due to an excess secretion of epinephrine. Holton,[1] however, reported that they secrete both epinephrine and norepinephrine. These observations were confirmed by Goldenberg and his co-workers[2] and they have shown that in a fairly large number of cases the norepinephrine excretion may range from 50 to 90 per cent of the total catechols present. A continued study by them again showed a marked difference in the effect of these substances in normal humans. With epinephrine there was an increase in cardiac output with a fall of over-all peripheral resistance. They postulated that there was a vasodilation of the vascular bed of the muscles which outweighed the vascular constriction of the skin, mucous membranes and the splanchnic area. They found an uniform increase in the heart rate. There was an elevation of the glycogenolytic rate and of the basal metabolism. With norepinephrine, in contrast, there was little change in cardiac output, but a constant significant rise in over-all peripheral resistance. There was less or little effect upon the pulse rate, the glycogenolytic rate and the basal metabolism. They found that when both catechols were simultaneously

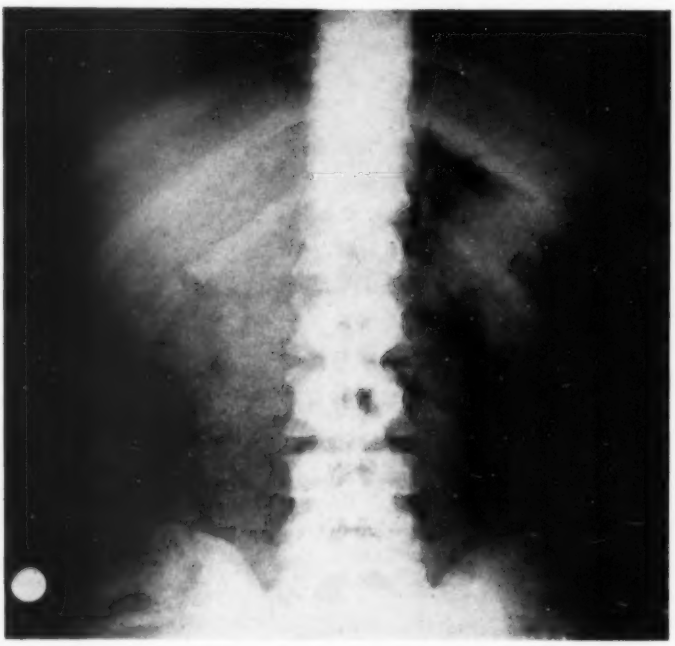

Chart 3. An air insufflation x-ray in a case of a pheochromocytoma arising from the left adrenal and growing in front of the left kidney. The low density of this tumor is beautifully brought out by the perfect circle of air outlining the tumor and that the upper pole of the kidney can be seen through the much less dense tumor. Most pheochromocytomas are of similar low densities and often give a negative shadow so to speak, rather than the denser positive shadows seen with adrenocortical tumors.

infused in equal amounts, their cardiovascular actions were antagonistic rather than augmentive. The vasoconstrictor action of norepinephrine was either nullified or over-balanced by the over-all vasodilator action of epinephrine. The clinical effects of their studies were striking. A normal subject receiving an infusion of norepinephrine, sufficient to produce a well marked increase in both diastolic and systolic blood pressure was mostly completely unaware of his blood pressure changes, and resembled in this respect a patient with essential hypertension. Whereas in contrast, infusions of epinephrine were almost always accompanied by headache, palpitations and an unpleasant feeling of anxiety and sweating. From these studies it can be reasoned that the secretion of various amounts

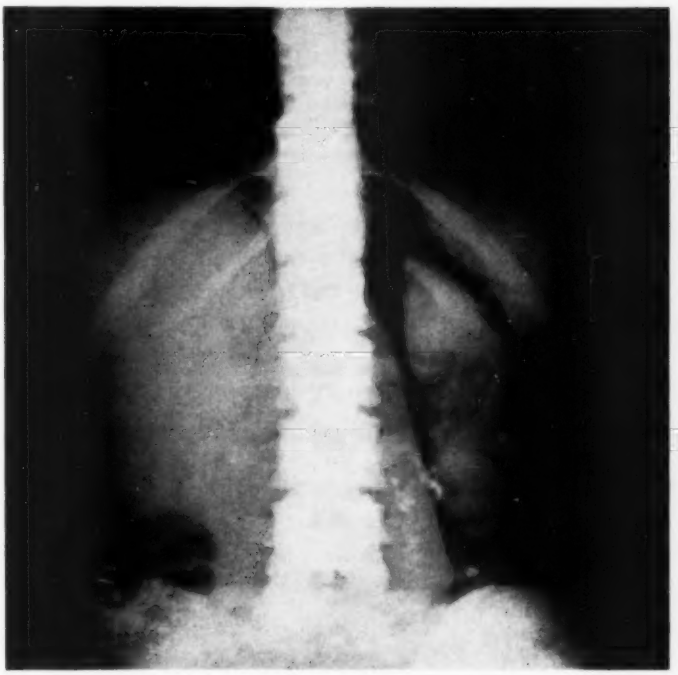

Chart 4. An air insufflation x-ray showing a large and somewhat denser tumor above the right kidney. The air outlines the left kidney beautifully but the fascial spaces on the right are pressed upon firmly by the tumor so that the air does not infiltrate very well.

of these active principles may produce a wide range of clinical phenomena. Such has occurred with these tumors and the variables were without explanation until these experiments were reported.

Symptoms

The symptoms may be simply classified into the silent, the paroxysmal, and the continuous hypertensive.

The Silent: An individual may go through life with a pheochromocytoma and never experience any effect of its presence. It may be discovered accidentally by x-ray, at operative exploration or at autopsy apparently unrelated to the cause of death. Fatal intraperitoneal hemorrhage has occurred with right adrenal tumors, also without any other symptoms.

These tumors from section and assay contain both pressor catechols but in some fashion, whether in the absence of a trigger release mechanism or some reason of the situation of the tumor, the individual gives no history of any relating symptoms.

In some, without symptoms, death may occur with a slight trauma. Again a pressor attack may occur with an operative procedure unrelated to the tumor. Not infrequently an anesthesia has precipitated the pressor attack in an unsuspected case. The occurrence of such pressor attack, if possible should cause abandonment of the operative procedure until the cause of the pressor attack has been ascertained.

The Paroxysmal: The first description of the syndrome was that of "paroxysmal hypertension." This is not always indicative of a chromaffin tumor. Similar crises have been described in eclampsia, lead poisoning, essential hypertension, nephritis, aortitis and various diseases of the nervous system such as epilepsy, traumatic or vascular damage to the brain or the meninges and also in tabes dorsalis. Tumor apparently has not occurred with these disorders. However most people who have a tumor with paroxysmal symptoms have been treated usually under various diagnoses until the true cause was ascertained. These were essential hypertension, cardiac neuroses, hyperthyroidism, diabetes mellitus and renal tumor.

The paroxysmal hypertension occurs in 30 to 40 per cent of the known tumor cases. When the attacks occur they are acute, unpredictable, and lasting from a few minutes to several hours. The palpitation and headache may overshadow the other symptoms. There is apprehension, anxiety and restlessness. The extremities may become cold and pale. There is an increase in the pulse and a marked rise in both systolic and diastolic pressure. The attack ceases with marked sweating, fall of blood pressure and a feeling of exhaustion. There is often a rise in the blood sugar and the appearance of glycosuria. Hypermetabolism is present as well as some changes in the electrocardiograph. With a complete picture of such a clinical phenomenon in an apparently normal individual, the diagnosis is often tenable and then with specific tests the presence of a secreting tumor may be proven. The attacks are most often similar each time, but may slowly increase in frequency, severity and duration, progressing with the growth of the tumor.

A differential diagnosis of tumor from psychoneurosis and hysteria offered difficulties in the past until the specific tests were devised. In

children there have appeared paroxysmal crises associated with metabolic reactions, but with no tumor present. Some of these resemble the disturbances in the diencephalon described by Penfield.[3] As a rule since paroxysmal hypertension was the symptom first described and apparently "labeled" as pheochromocytoma, the large number of these cases are those in which provocative tests have been frequently used and these cases are not usually missed.

The Persistent Hypertension: It is most likely that by the time a diagnosis is arrived at, persistent hypertension is the more frequent type of hypertension seen with a tumor. This is supported by Green[4] who has shown that over 70 per cent of his collected cases had more or less continuous hypertension. It is in the large group of persistent hypertensives seen that a special effort must be made to exclude pheochromocytoma. What hypertensives should arouse the suspicion of pheochromocytoma? First, hypertensives who have at times symptoms suggestive of crises; second, all those hypertensives who have an elevated basal metabolism; third, a hypertensive who also has at times an elevated blood sugar and glycosuria; and fourth, those hypertensives in addition who have associated severe sweating. The presence of most or all of these symptoms requires the use of a specific test to eliminate pheochromocytoma.

A persistent hypertension may occur with no suggestive symptoms and still in a rare case be associated with tumor and cured by the removal of the tumor. Certainly before any severe operative attempt at correction, as a lumbo-dorsal sympathectomy, is undertaken, all persistent hypertensives should be given a trial run with Benzodioxane or Regitine.

Specific Tests

Provocatives: Histamine: Roth and Kvale[5] reported the use of intravenous 0.05 histamine base to precipitate the secretion of an excess amount of pressor substance in pheochromocytoma. They showed that with tumor, after a short initial drop, there was a marked rise in systolic and diastolic pressure with all the symptoms of a pressor attack. The reaction is short and the blood pressure returns to its former levels. Repetition produces similar results. The test should be given only in a patient without sedation. This test when properly performed, when tumor is present, is very reliable and its value has been repeatedly confirmed. A few cases have given a negative reaction and later proven to have tumor, with as

yet no clear explanation. In hypertensives without tumor, especially in psychoneurotics, a reaction has been seen resembling that of tumor but with a slower rise and of more sustained and prolonged duration. The possibility of excess catechols causing such a reaction awaits investigation. In some tumor cases with severe reactions due to the size of the tumor, the use of histamine must be guarded and Regitine must be available to prevent a catastrophy.

Mecholyl bromide, introduced by Guaraneri and Evans[6] in doses of 25 mgm. subcutaneously will incite a paroxysm of hypertension in patients with pheochromocytoma. The accuracy of this test has been confirmed by others as well as by ourselves. H. Aranow, Jr.[7] modified the test for safety purposes by including .001 gm. atropine sulfate parenterally previous to the test to prevent serious reactions that may occur unless the parasympathetic effectors are previously blocked.

Etamon (tetraethyl ammonium bromide) reported by LaDue and his co-workers[8] produces a paroxysmal rise in the blood pressure in pheochromocytoma. The advantage of the test is that the extent of the rise may be controlled by changing the position of the patient. It is a longer acting agent than histamine and has been stated by Roth to be less reliable.

We have found all three provocatives reacting as described in cases where tumor was proven and that after removal of the tumor, all three had no reaction. We have had a greater experience with histamine and because of the experience believe that it may be more reliable. The variables of the reaction are shown in the accompanying chart.

Antagonists: Benzodioxane (piperoxan) introduced by Goldenberg,[9] the first used, has had a wide use and its value established. It is of importance in distinguishing persistent, essential hypertension from the continuous hypertension seen with pheochromocytoma. In a patient with the tumor, the drug is introduced intravenously and has a predominately depressor effect in which both systolic and diastolic blood pressure falls significantly and rapidly and soon returns to or above its previous reading. In patients with blood pressure elevation due to other reasons besides pheochromocytoma, there occurs no change or a pressor change in which the blood pressure rises. In these there may also occur flushing and tachycardia. The accuracy of Benzodioxane has been well established. There have been several cases reported in which a positive reaction was obtained and no pheochromocytoma found. Cases have been

reported with no reaction in paroxysmal hypertensives with tumor when injected in the quiescent state. This is the expected reaction in those instances. Conley and Junkerman[10] reported a negative reaction in a continuous hypertensive and a proven tumor. It may be assumed that other pathological conditions may be present that have influence upon the pressure changes. Since the depressor effect of Benzodioxane is only effective when the elevated pressure is due to the presence of excess catechols and to date excess catechols in the blood in quantities have been seen only in association with pheochromocytoma, the specificity of the test must be recognized.

Dibenamine (NN dibenzyl betachlorethyl amine) was first used for study on man by Hecht and Anderson.[11] This drug was shown to have marked sympatholytic effect upon the muscle nerve endings in the smaller arterioles. This marked over-all depressor effect may last for twenty-four to forty-eight hours. During the period of depressor effect, the sympathetic system may be unresponsive to the necessary pressor catechols to prevent a complete collapse. This drug has not been used for diagnosis because it has a depressor effect in both normals and in the hypertension of pheochromocytoma. Its use has been mostly confined to the therapeutic control in operative procedures.

Regitine (C_{7337}) reported by Grimson and co-workers,[12] is used both for its diagnostic help and as a therapeutic aid at the time of operative removal of the tumor. It produces a more pronounced and more prolonged reduction in blood pressure than Benzodioxane when used for diagnostic purposes. Its therapeutic effect is more effective than Dibenamine because it is less toxic and more easily controlled. False positive tests have occurred in cases with uremia. The administration of Regitine may be intramuscular or intravenous.

Experience with these three drugs has shown the value of both Benzodioxane and Regitine each within a specific area and it is most probable that they will be in continued use, unless supplanted by the estimation of the catechols in the urine.

Demonstration of Pressor Substances: The first report was that of Ernould and Picard in 1934[13] who claimed they identified a pressor substance chemically in the blood of a pheochromocytoma. Beer et al.[14] demonstrated pharmacologically a pressor substance in the blood of a tumor case during a hypertensive crisis. These two methods have not been of value in the diagnosis and some doubt has been raised as to the

interpretation of the tests. The tests as described were also too difficult for ordinary use.

More recently the identification of the pressor substances and a fair quantitative estimation of the various catechols have been done upon the urine in normals, the urine of ordinary hypertensives and the urine of the pheochromocytomas, both paroxysmal and with sustained hypertension. The use of various methods has been investigated by Goldenberg[15] who after experimenting with bio-assay and pharmacological methods, used an alum hydroxide extract and concentration of the 24-hour specimen of urine and by florometric determination found that in normal people it was not simple to separate the two catechols but estimated that roughly 10 per cent appeared as epinephrine and 90 per cent plus as norepinephrine and that the total was somewhere between 20 and 50 gamma (micrograms) in twenty-four hours. In essential hypertension he found excretions up between 75 and 100 gamma in twenty-four hours. The important great difference appeared in the sustained hypertension due to pheochromocytoma in which excretions varied from 600 to 2700 gamma in 24 hours. The paroxysmal cases varied, according to attacks or not, from 110 gamma to a top of 580. A report of this study is to be shortly made by Goldenberg. The simplification of the test for the excretion of the catechols in the urine and the preliminary report of the amounts eliminated in the various conditions if verified by experience, offer a simple and real positive diagnosis of the syndrome and will probably see the abandonment of the present chemical tests.

Radiography: In any hypertensive, the visualization of a tumor in the adrenal or in the area of a sympathetic ganglion strongly suggests the possibility of a chromaffin tumor. With a characteristic history and with positive specific tests, the visualization of a tumor is the next important step. A large tumor may show a shadow upon a plain abdominal film but this is rare with pheochromocytoma because they are usually of very low specific density, almost similar to cysts. Also most all the cases of pheochromocytomas do not have much fat, the syndrome producing loss of weight. Calcification is not frequently seen in these tumors. Pyelography has shown displacement of the kidney downwards by a tumor mass and in some a flattening of the upper pole of the kidney. Retroperitoneal gas as a diagnostic aid in localization of these tumors has now been used for years. First used perirenally through the flank by ourselves[16] and others in many cases, it has been used from the first to identify the

tumors on a film clearly. More recently the use of gas by the presacral route, introduced by Rivas,[17] has popularized the method. In a small tumor there is no better method than that of retroperitoneal gas. It must be stressed, however, that the demonstration of a pheochromocytoma is often of an ovoid or circular shadow less dense than the other tissues and the opposite of the adrenal cortical tumors which most often are dense like renal tissue. Extra- adrenal pheochromocytomas have been outlined by retroperitoneal gas. In several cases in which the tumor was near the aorta and under pressure, failure of the gas to infiltrate into that region suggested the probable site of the tumor. Interpretation of retroperitoneal gas insufflation films needs experience in order to be correct. Laminographic x-rays have successfully shown these tumors. We have had many confusing shadows with hypertension in cases with negative specific tests. Exploration of some of these showed the shadows to have been due to a retroperitoneal spleen displacing the kidney or a pancreatic cyst across the pole of the kidney and several times a retroperitoneal lipoma. Aortograms, first used to show an adrenal tumor by dos Santos, have been used by others and ourselves and have been of less value to date than retroperitoneal insufflation gas x-ray. Venograms have been reported as used by Goodwin.[18] Most of these tumors have been almost cystic and of no uniform pattern of vascularity and, with expansion of a venous system without the tumor and from our vascular studies, we have not had the assurance in interpretation that is present in the round or ovoid mass defined by gas. The intrathoracic tumors have been all clearly shown by x-ray, the lung conveniently supplying the contrasting air. Because of the possibility of an intrathoracic tumor being present, all cases of suspected pheochromocytoma should have such films made.

Therapy

The treatment of pheochromocytoma is complete removal of the tumor or tumors if more than one is present. If completely removed, the patient is relieved of all symptoms and signs. The success of the operation is due to the planning of the procedure. Two adrenolytic agents have been used for the therapeutic effect in the operative handling: Dibenamine and Regitine.

Dibenamine has been used in amounts of 5 to 7 mgm. per kilo of body weight given in an infusion of 300-500 cc. of saline slowly for one hour. The action is a sympatholytic effect up to forty-eight hours.

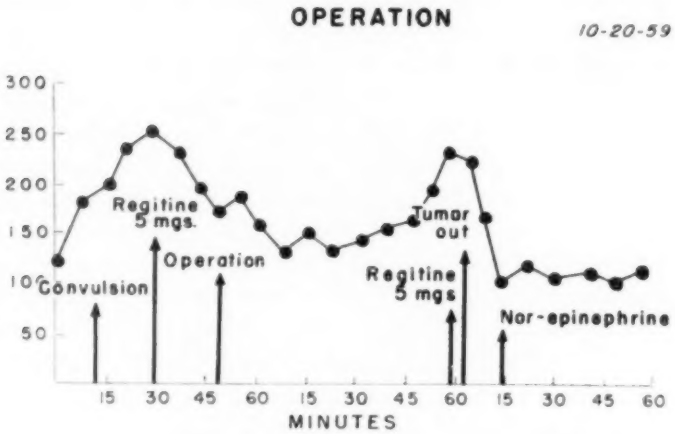

Chart 5. The operative chart of the removal of the tumor seen in chart 3. This large tumor with a severe paroxysmal type syndrome had severe convulsions on beginning of the anesthesia which were controlled by Regitine and later the drop in blood pressure after removal of the tumor was controlled by norepinephrine.

It has been used with severe cases of hypertension with pheochromocytoma, preoperatively to condition the patient for operation. During the prolonged action of lowered pressure, the patient is free from hypertensive crises, rests and improves with nourishment. So used, marked improvement has occurred in severe cases where emaciation and exhaustion have been present. The beneficial effect of Dibenamine has been reported by Spear and Griswold, [19] by Hoch,[20] by Cahill and Montieth[21] and others. Side effects of the drug may occur and cause cessation of the treatment; partial hemiplegia and loss of sensation have occurred, both temporary. Tetany has occurred, relieved by calcium gluconate. It has been customary to proceed with the operative effort at the later part of the period of the depressor effect. While this effect is still present, manipulation of the tumor is possible, without the sometimes fatal effect of excess catechols. However, operation during the maximum pressure effect eliminates a diagnostic aid, namely the rise in pressure that occurs in the handling of a tumor of pheochrome tissue. In addition the use of Dibenamine has a major risk, in that on removal of the tumor a marked fall in blood pressure usually occurs and this fall may be reversed by norepinephrine, but in the presence of Dibenamine, such reversal is not

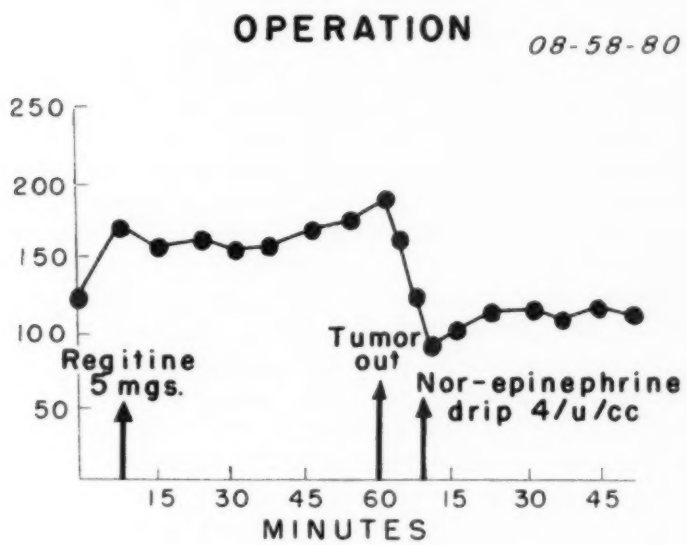

Chart 6. The operative chart of the case with x-ray in chart 4. A less severe case in a woman after childbirth in which one injection of Regitine and post-removal norepinephrine were needed.

possible and death may occur. Because of these effects, there is a necessary regulation of the timing in the injection of Dibenamine in relation to the operation. Enough effect must be present to allow manipulation of the tumor, but not too much to prevent the use of sustaining drugs. Use of Dibenamine is probably too risky compared with the safety and effects of the other adrenolytic drug, Regitine.

Regitine C-7337 (2(N-p-tolyl-N-(m hydroxy-phenyl)-amino methyl)-imidazoline hydrochloride) introduced clinically by Grimson and his co-workers,[12] given intravenously an hour or two before operation, in a 5 mgm. dose and then given intravenously during operation in a dosage of 0.08 to 0.33 gm. for each kilogram of body weight, to prevent paroxysms of hypertension, tachycardia, respiratory depression or convulsions or other effects of epinephrine intoxication, has apparently to date been the most satisfactory adrenolytic agent in operative procedures. It definitely has been safer and more satisfactory than Dibenamine. After the tumor is removed under Regitine administration, and the pressure falls, a reversal of this fall is possible by the administration of norepine-

phrine because Regitine will completely suppress the effect of epinephrine, but only partly the effect of norepinephrine.

The anesthesia problems in these chromaffin tumors[22] have been largely concerned with four important elements: adequate relaxation, the possibility of pneumothorax, the physiological effect of excessive secretion of epinephrine or norepinephrine during the manipulation of the tumor, and the sudden circulatory depression following its removal; no matter what the anesthestic regime, anoxia is to be avoided. Anoxia appears to be as potent a stimulant to medullary secretion as is tumor manipulation. Agents, which in the presence of epinephrine produce serious ventricular arrythmias are to be avoided. Cyclopropane, chloroform, and ethyl chloride are unwise choices for anesthesia. Basal avertine, ether and oxygen have been most frequently used.

Surgical removal of these tumors has been done successfully by all routes. These have included flank extraperitoneal approach without or with rib resection, either bilateral when the tumor has not been properly located, or unilateral if located. Thoracico-abdominal approach, as well as rib-flap retroperitoneal incisions, enjoyed a vogue for a while. Because of the possibility of these tumors being multiple (16 per cent) and because of their variable locations, the transverse, transperitoneal upper abdomen has in our hands been the most satisfactory approach. This has been especially so in the past in which with an original flank approach multiple tumors required two operative procedures for their removal. Experience since has enabled us to remove all the tumors at one stage with the transperitoneal approach. The value of adequate exposure is obvious, and with a wide exposure the blood supply to and from the tumor is easily severed before manipulation of the tumor. In large tumors, especially on the right side and if close to the vena cava, soft occlusion clamps may be necessary on the cava, above and below the tributary veins, before the tumor is handled. After removal of the tumor, the blood pressure often falls to surprisingly low levels, and this may be prevented by using an increasing amount of norepinephrine intravenously (.4 mgm. norepinephrine in 1000 cc. of saline). In two cases of pheochromocytoma associated with Cushing's disease, the patients were prepared in addition with high salt intake and desoxycortisone, which was the only adrenal steroid available at that time, and the operative procedure was successful. These tumors are usually in a fairly vascular bed and if large, control of hemostasis may be difficult and may require blood replacement.

CHART 7—PHEOCHROMOCYTOMA

Name	*Hosp. No.*	*Age*	*Year*	*Side and Type*	*Results*
J.B.	59936	59	1924	R—malignant	DIED—no operation
E.W.	312177	33	1932	L—benign	DIED—no operation
S.P.	438208	53	1934	R— "	DIED—postoperative
D.P.	542008	27	1938	L— "	" "
G.K.	41024	61	1939	R— "	" " spontaneous tumor hemor.
E.C.	600888	49	1940	R— "	cured
J.S.	657128	48	1941	R also Cush.	"
P.H.	690134	29	1942	R+Zuckerkandl	"
H.A.	623060	25	1943	R	no operation
D.B.	815439	10	1946	R+Zuckerkandl	DIED operation
J.L.	716125	13	1944	L+Retroperit.	cured
P.D.	844975	12	1946	R+Thoracic	"
K.G.	857560	42	1947	R	"
M.E.	965960	49	1949	L	"
H.B.	967974	41	1949	L	"
R.H.	085580	31	1952	R	"
A.G.	102059	26	1952	L	"

A chart summary of 17 cases of pheochromocytoma at the Presbyterian Hospital showing that in the beginning the disease was unrecognized and of course no attempt to save the patient by operative intervention was made. Next the disease was not diagnosed but operative attempts were made to correct a hemorrhage or a collapse without correction of cause. Later the condition was recognized and corrected with only one death in 1946 and none since. Specific diagnostic tests were used and chemical control of the operative procedures was used.

The tumors are bright pink red, soft, elastic and cystic. The weights vary according to size; and the tumors contain varying amounts of norepinephrine and epinephrine. After recovery has been accomplished and discharge is contemplated, a histamine test has been routine to show that no tumor tissue had been overlooked.

SUMMARY

The diagnosis of pheochromocytoma may be made by: (a) History and specific tests; (b) estimation of catechols in the urine; (c) demonstration and location of the tumor by gas insufflation x-rays.

The only successful treatment is operative removal. This has been made successful by: (a) An adrenolytic agent to prevent hypertensive

crisis on handling the tumor; (b) a replacement sustaining hypertensive substance to correct the hypotensive state that follows a removal.

The risk in these patients is in the operative procedure phase. The removal of the tumor cures the pressor syndrome and the prognosis is good in the large number of benign lesions.

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HORMONES AND THEIR INFLUENCE ON THE EMOTIONS*

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THE advent of modern clinical endocrinology, with Brown-Sequard's experiments upon himself in 1889, gave new impetus to an age-old quest. Man has sought for eons to explain his behavior, and correlative with this, he has looked for ways to modify it. The accumulation of natural and synthetic hormones within our time, the welter of animal experimentation, the weight of years of clinical medical documentation, seemed to offer the magic touchstone. Here, surely, at long last, was the lever with which to move man's world.

Since the second century A.D., when Galen postulated the doctrine of temperament, it had seemed reasonable to suppose that the traits, habits, characteristics, even the attitudes and values displayed by man, were intimately related to his physiology. Hence the facile conclusion: To alter physiology is to alter psychology.

William James,[1] a contemporary of Brown-Sequard, contributed a leaven to this logic. A man's life, he suggested, is, in its widest possible sense, "the sum total of all that he can call his, not only his body and his psychic powers, but his clothes and his house, his wife and his children, his ancestors and friends, his reputation and works, his lands and horses and yacht and bank account." And James added the sweeping observation: "All these things give him the same emotions."

However this may be, it becomes apparent at the outset that only in the context of the whole man can the influence of hormones on his attitudes and behavior be rightfully assessed. For man's behavior comprises factors that are sociologic and economic–cultural, as well as anatomic and metabolic-physiologic. Farther down the phylogenetic scale, behavior is more rigidly determined, hence more predictable. Nevertheless, experimental data on hormones and behavior serve as a useful interpretive baseline. Beach[2] has reviewed these data exhaustively. His are the

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conclusions of the laboratory scientist, and they are in line with the affirmations repeatedly made by the clinical psychiatrist during the last three generations: Hormones are only one of several factors operating in conjunction to produce a particular pattern of behavior under particular circumstances. In most instances, the final form of overt response in the human is controlled to a greater degree by factors in the external environment than by hormonal variations in the internal environment.

Ample data support the assumption that in the complex relationships and events governing human behavior, the elements of magnitude, duration and time of change in the hormonal tide are of great significance. Observe, for example, the treatment of cretinism by replacement therapy, which does much to correct the classic consequences of the thyroid deficiency, yet often fails to remedy the profound emotional and intellectual defects observed in these patients. While this observation in no way minimizes the importance of thyroid extract in the treatment of cretinism and the almost miraculous results which may be obtained, it demonstrates that the correction of the metabolic disorder does not of itself insure normal mental function.

Psychotic reactions may be an accompaniment of hypothyroidism. Prominent in these reactions are lethargy, retardation and defects in mental acuity. These are, however, by no means unique to, or pathognomonic of, the psychoses associated with myxedema. Even superficial inquiry demonstrates that the more elaborate and significant aspects of the psychiatric symptoms are determined by the prepsychotic personality of the patient. A similar state of affairs exists in hyperthyroidism. Emotional behavioral disorders are frequent accompaniments of this disease, and there are more or less distinguishing symptoms: overactivity, irritability, lability of affect, and acceleration of ideational processes. Yet whether thinking is paranoidal or confusional, affect elated or anxious, behavior controlled or restless to the point of hypomania, these features are derivatives of the fundamental organization of the preillness personality.

Then, too, there is no strict correlation between the degrees of metabolic hypo- and hyperfunction and the psychiatric symptoms which accompany them. Often psychiatric symptoms are the first observable signs of the illness. Occasionally they become evident only after treatment has begun. Indeed, all clinical types of psychologic response are

possible in myxedema and hyperthyroidism. Most frequently, the only psychiatric change clinically perceptible is an intensification of the pre-existing mode of psychologic adaptation. Hence the range of possible adjustments, from adequate through neurotic to a frankly psychotic state. Here, again, it must be emphasized that physiologic remedy of the pathologic metabolic state is no guarantee that the clinical psychiatric picture will recede with equal celerity.

All this evidence serves to underscore the absence of an invariant relationship between hormones and behavior. Among the determinants of type of response, genetic factors play an important part, but the one-to-one correlation so often reported in animal experimentation is certainly not true of the human. Even in animals, as Beach points out, androgens facilitate *croaking* in the male frog, *crowing* in the rooster, *cooing* in the cock pigeon, and *calling* in the male cat. In homologous fashion, the psychodynamic potentialities of the human may be fulminated by exceptional hormonal events into clinical expressions characteristic of the patient.

The timing of these pathologic events is of major importance. Thyroid deficiency in the newborn is a recognizably different entity from that seen in juvenile and adult myxedematous patients. This merely serves to exemplify what is physiologically self-evident: that a catastrophic metabolic occurrence, such as the withdrawal of the influence of certain hormones, has an effect upon the organism modified by age. The prepubertal castrate differs from the senile castrate, not only in physiologic and anatomic organization, but also in psychologic adaptiveness.

Moreover, the ease and certainty with which desirable intellectual, affective and behavioral changes will follow replacement therapy differ widely at different ages. Obviously, external environmental forces are modifying influences. As the preacher so cogently observed about life processes in general: "There is a time . . ." The psychodynamic organization of the individual may make him vulnerable to stress at a propitious time in his life cycle; at another time he may be virtually immune to such experience.

Lidz and Whitehorn[3,4] in investigating the relationship between severe emotional shock and onset of hyperthyroidism, were not surprised to find emotional stress as a causative factor in a clinical picture which mimics the expression of fear and terror. They conjectured that the thyroid gland plays a role in physiologic mobilization for prolonged

stress. This role remains to be clarified. The patients described by Lidz and Whitehorn appeared to be reacting to a threat of disruption in the dominant interpersonal relationships upon which their security depended. To them, the threat was catastrophic. The personalities of these patients were dissimilar in many respects, yet certain critical attitudes were common to them all. They were inordinately insecure, and their stability seemed to depend upon their success in gaining affection by the expedient of self-sacrifice. Their intense need for affection and attention made catastrophe inevitable.

In the experience of Ruesch and his colleagues,[5] patients with thyroid disease are abnormal in the sphere of their socio-psychological relationships. Fifty-four per cent of the patients studied by them were characteristically "pushers" or "climbers" and the *anlage* of the illness could be traced to an insecurity of the home situation. The onset of the actual breakdown coincided with environmental maladjustment.

Endocrine dysfunction has another attribute of concern to psychiatry. In contrast to "normal" individuals, patients with evidence of hypo- or hyperfunction of the endocrine glands seem to be more or less vulnerable to stress of any kind. Even the rapid change from a level of hypofunction to one of normal function is frequently accompanied by an emotional disturbance of major proportions. Here, again, the pattern of emotional disturbance depends on one set of circumstances, while the fact of its appearance depends on another. It would appear that the truly significant happening is the fact of change itself. The capacities of the homeostatic buffering forces, as it were, have certain limits; when, in the wake of subliminal changes, these limits are approached, the ability of the organism to withstand further change is taxed seriously. Hence, at this point, what would otherwise be an easily tolerated stress may be sufficient to disrupt the equilibrium of the individual. The ensuing reorganization of personality may differ radically from the previous pattern.

A few clinical illustrations of this phenomenon may be apropos. We have observed, as have others, the frequency with which a patient with Addison's disease is seemingly precipitated into an acute psychotic episode after the institution of hormonal treatment. Despite the fact that the adrenocortical deficiency is remedied, the electrolyte imbalance corrected, the abnormal pattern of steroid excretion altered in the direction of normal, the patient displays a gross psychosis. Delusional

thinking, with commensurate modification of affect and behavior, is evident. This development is in striking contrast to the relatively normal behavior of the patient during the state of acute adrenocortical insufficiency. With continuation of therapy, however, the untoward psychiatric phenomena are corrected spontaneously.

Similarly, in Cushing's disease, when the hypercorticism is corrected by surgical removal of the adrenocortical tumor, or of most or all of the hyperplastic cortices, there is observed in some patients a period of profound psychiatric disturbance which appears to be independent of any demonstrable physiologic imbalance. It would seem that with the rapid shift in level of physiologic adaptation, the over-all pattern of psychologic adjustment has been modified comparably. The impression obtains that this is an over-all pattern effect and not the result of aberration in a single hormonal or metabolic modality.

Thus, violent shifts in the internal environment constitute as much of a psychologic stress as do comparatively traumatic disruptions in the external environment. The time required for emotional adjustment to these great internal environmental changes is sometimes considerable. During the interim, psychologic defense mechanisms typical of the individual are mobilized and they constitute the clinical psychiatric picture.

With regard to the hormonal-emotional relationships in the middle life of the male, much disagreement prevails. Werner[6] described a group of fifty-four male patients, each of whom had some form of testicular hypofunction or afunction, and he suggested that such dysfunction could be instrumental in producing hypogonadal or male climacteric syndromes. Here is one attempt to relate hypogonadism directly with the climacteric. However, Heller and Myers[7] are impressed with the rarity of the climacteric syndrome in men who live to old age. Simpson[8] thinks that the male climacteric is physiological but that the complete syndrome is relatively rare. In our opinion, there is no cogent evidence that hypogonadism and glandular dysfunction are the cause of the depressions which occur in the male in middle life.

That hypogonadism is compatible with normal behavior is an observation of long standing. Two decades ago, Hackfield[9] made an interesting report on the therapeutic castration of forty males following various criminal sexual offenses. In some of the older men, the operation had been performed twenty-five years previously. In general, these individuals showed no serious psychiatric symptoms. A few had demon-

strated a passing tendency to mood swings but these were short-lived and in most of them other possible causative factors were operating. There was no high incidence of depression among these individuals, and actually Hackfield believed that the neurotic rate was no greater than that in a sampling of the "normal" population. Each of these individuals had apparently also become a useful citizen.

Several years ago, Greenhill[10] deplored the widespread tendency to assume that any woman within the age group of forty to fifty-five, who complains of nervousness or displays a psychiatric disorder, falls into the menopausal group. On the basis of a study of 300 patients, Greenhill was impelled to feel that there is no justification for the term "menopausal syndrome" if the term by definition includes a psychiatric disorder. He noted further that the metabolic instability consequent on failing ovarian function has its paramount effect upon the autonomic nervous system, which is involved in the common symptom of the "hot flash." It was his conclusion that the majority of women experience no symptoms of a psychiatric nature during the menopause and manage without difficulty any mild symptoms of autonomic over-reactivity. Parenthetically he noted, as have other psychiatrists, that pre-existing psychoneuroses may be exacerbated at the time of the climacteric and that estrogen therapy will not relieve these psychoneurotic symptoms.

In 1948, Danziger and Kindwall[11] treated nineteen patients with various psychoses, including schizophrenia, and five psychoneurotic patients, with large doses of thyroid extract administered over a long period of time. These investigators suspected that cerebral anoxia was a prerequisite for the development of psychiatric disorder and they were endeavoring to combat the hypothetical anoxia by increasing basal metabolic rate from low or low normal to high normal or somewhat higher levels. Their clinical results with thyroid were startlingly good. Yet when thyroid extract therapy was applied by other investigators in psychotic patients, the results were uniformly disappointing.

Relatively little further attention was paid to this report until 1950, when Hemphill and Reiss[12] described investigations which seemed to support the ideas of Danziger and Kindwall regarding the etiological role of anoxia in schizophrenia. That same year, Ross McFarland,[13] after a carefully controlled, scientific study of anoxia, stated categorically: "Conclusive evidence is yet to be obtained that impaired oxygenation is of primary importance in schizophrenia." Obviously, further painstaking

studies will be required before a definitive statement can be made concerning the usefulness of thyroid substance in the treatment of the functional psychoses.

There is a voluminous literature implicating the adrenal glands in the etiology of schizophrenia, but little agreement as to their precise role and its significance. Hoagland[14] hypothecates a qualitative abnormality of adrenal responsivity in schizophrenics. It is his observation that ACTH fails to elicit a normal response in these patients. He believes, therefore, that if the adrenal function of the schizophrenic patient could be restored to normal, prognosis in the disease would be improved. Some authors share this view; others, including Altschule, Hemphill and Reiss, are unable to confirm it. Possibly, different steroid compounds mobilized from the adrenal cortex in response to factors as yet unknown are responsible for the different phenomena witnessed by these investigators. Possibly, in some patients these functions are irreversibly impaired. Pending the completion of further research, it may be wise to admit with Selye[15,16] that there is no convincing evidence at the present time to substantiate the assumption of an adrenal substrate for schizophrenia. As Selye observes, numerous forms of psychologic and physical stress have been considered as precipitating factors, and it would be tempting to correlate them with the adreno-cortical insufficiency so often observed in this illness. However,whether adrenal aberration is the cause or the result of the mental disorder with which it is allegedly associated, remains to be established.

Another important problem relating to the physiologic effects of hormones upon emotions and behavior is the role they play in influencing body image. This problem is extremely complicated, and except for the work of Rome and his co-workers, has been largely neglected.

Obviously, the phenomenon of pubertas praecox can wreak psychologic havoc. Whether any of the untoward emotional effects can be ascribed to the hormonal changes per se is a moot question. To develop breasts and pubic hair, to begin to menstruate, imposes upon the young child environmental consequences of the first magnitude.

The psychology of being different, of looking different, has widespread ramifications. With the development of adrenocortical virilism, emotional defenses are soon displayed by the victim. Social withdrawal, shyness and a generalized inability to permit a normal unconscious feminine identification, supervene. The anxiety and insecurity aroused

by the visible abnormalities often serve to intensify ordinary difficulties of psychosexual maturation. The indirect influences of the morbid picture on parents and siblings are considerable. Guilt on the part of the former, with over-solicitude and unconscious rejection, intensifies whatever psychopathologic tendencies may exist in the family constellation. The heightened sibling rivalry created by preferential treatment on the part of parents is superimposed on the girl's feelings, both conscious and unconscious, of being an ugly duckling. Facial hirsutism and other anomalies characteristic of the condition may become real barriers to free and easy social relationships with friends and schoolmates. The effects of such thwarting influences may be profound. In self-defense there develops, as a rule, an increased investment of emotion in the physical person, together with a displaced, excessive erotization. The resulting conflicts are predictable.

When to these conflicts are added anatomic deviations, such as a phallus-like clitoris or an actual misidentification of sex, as in the instance of male pseudohermaphrodites, a bad psychological state becomes worse. In the opinion of Rome, the frequency with which precocious sexuality is reported as a prominent feature in these conditions, reflects multiple causation rather than a pure and simple manifestation of hormonal influences. Among the many factors to be considered, he lists the iatrogenic element as one of the most prominent.

These patients are of necessity brought to a heightened awareness of their genitals and breasts by the periodic medical examinations to which they are subjected. Their behavior vis-à-vis the medical help sought reflects to some degree the parental anxiety. There follows the business of securing multiple medical opinions. This entails multiple, extensive, and exhaustive examinations, with the inevitable undressing, manipulation, and comments advertent and inadvertent. Often surgery is discussed, for it may be indicated both diagnostically and therapeutically, and the quota of stress, with its attendant anxieties and defensive reactions, is thereby augmented.

These psychosocial forces are enough in themselves to create a bad psychological climate, but the miasma is intensified by the virtual loss of normal outlets susceptible of moderating everyday neurotic character traits. Social intercourse, which ameliorates anxiety, is denied these patients. Sometimes because they are different, but most often because, feeling different, they act it, the very thing which they have suspected

and feared comes to pass: they are rejected, snubbed, and even openly scorned by others. Hence, in this tangled web of hormones and behavior, it is literally impossible to distinguish the hormonal filaments or to determine their structural value.

Hermaphroditism and adrenocortical virilism are extreme illustrations, caricatures of events which take place in the more common glandular syndromes. Castration effects may be viewed in the light of these prototypical examples. Not only the physiologic trauma of orchiectomy or ovariectomy, but also the psychologic and sociologic deprivations which these impose upon the patient, subjectively or objectively, need to be assayed. In some instances, the psychologic symptoms which are said to be part and parcel of the surgical castrate, and are therefore attributed to low estrogenic tides and the like, are really the products of pure emotional conflicts which cannot be remedied by simple hormonal replacement therapy. The patient is confronted, for example, by the unmistakable evidence of barrenness; depending upon her personality, this can be a great threat to her femininity. Dyspareunia, vaginismus, depression, lassitude, insomnia, anxiety, and a host of other familiar concomitants, may well be regarded as psychologic and psychosomatic defenses developed by an exacerbation of long-existent, albeit latent, psychosexual conflicts.

If it appears that these illustrations of an erroneous assessment of the influences of hormones are patent because they are extreme, I would call to your attention the frequency with which the clinician is induced to treat the syndrome of obesity and neurasthenia with thyroid extract because of an alleged cryptic hypofunction. In most instances, this inducement is the product of a number of factors. Frequently, there is the patient's contribution, in the form of statements of a low basal metabolic rate "demonstrated" some time in the past and "remedied" by the administration of thyroid extract. Then, too, many of these patients have elaborated their own theories regarding their illness, theories which exclude the possibility that they might be emotionally upset. Their sophistication creeps into the "classic" history they give of sensitivity to cold, skin change, change in menstrual habit, sluggishness, a loss of former vigor and enthusiasm, and the like. When, added to this, comes objective laboratory documentation in the form of a borderline low metabolic rate determination and a mild secondary anemia, the hurried clinician is tempted to add two and two and get twenty-two. The neu-

rotic symptoms are then consonant with what has already been adduced.

Even in the absence of data which lend themselves to misinterpretation, the physician may be swayed by coercive efforts of which he is often consciously unaware. These may lead him to assume conclusions without due scientific dispassion. Often the "results" obtained in a post hoc fashion are attributed to the remedy of an "hormonal deficiency" which was actually non-existent. Many of the beneficial results seen in the treatment of these patients are derivatives not of hormonal treatment, but of suggestion, and ultimately of the physician-patient relationship.

Perhaps in a representative large practice, one encounters to an even greater degree male and female patients who loudly attest the efficacy of the hormonal treatment they have received. By and large, they are passive, dependent, insecure persons who are acting out their conflicts as well as attempting resolutions of them by recognizable neurotic techniques. For them, the displacement of purely emotional problems upon various aspects of physical function provides a more acceptable solution for difficulties than does a frank acceptance of the truly psychologic nature of the problem. Indeed, such displacement should not be thought of in terms other than an unconscious process of defense, for dynamically, such it is.

The while we shed light on the patient's problem, we have need to scrutinize our own contribution. I have the impression that in some circumstances the failure to recognize the more subtle manifestations of neurotic mechanisms prompts us to use these drugs as a last resort. Reliance on the potency of hormones is too often a facade covering our feelings of impotence and frustration when confronted by the demands of the patient for his kind of satisfaction.

In this general, admittedly sketchy review of an enormously complex subject, it is obviously impossible to do more than hint, infer and conjecture. Even so there are large lacunae. One of the more important of these concerns the vast body of data alleging direct cause-and-effect relationships between hormones and behavior.

For example, Gordon and Fields[17] treated human eunuchs with testosterone and reported that they became "psychologically more alert." Thomas and Hill[18] reported two cases of so-called involutional melancholia in the male materially improved following treatment with testosterone propionate. The suggestion is that the reduced androgenic level bears a direct relation to the abnormal mental state.

The very usage of the term "involutional melancholia" for a psychiatric entity implies that the endocrinologic change occurring at this time of life is the etiologic sine qua non. In order to balance the picture impartially, various and sundry personality disruptions have been ascribed to the male climacteric, as previously mentioned.

Such inferences are not only gratuitous, they are based on rather isolated fragments of evidence and fail to incorporate a truth of which Aristotle was cognizant. He said, and it is most germane:

> "There is however one peculiar inconsistency which we may note as marking this and many other psychological theories. They place the soul in the body and attach it to the body without trying in addition to determine the reason why or the condition of the body under which such attachment is produced. This would seem however to be a real question calling for solution."
>
> "PSYCHOLOGY," 1, 3, pp. 22-23
> (WALLACE'S TRANSLATION, 1. 35)

If any doubt lingers in our minds regarding the importance of the influences of emotional states upon body metabolism, confirmation of this importance may be found in the work of many investigators outside of our own specialty. In this connection, the conclusions of the anatomist and endocrinologist, G. W. Harris,[19] are of great significance. He states: "One of the striking facts emerging from recent work is the emphasis on emotional and psychological factors in the control of endocrine secretion. The relationship between emotional stimuli and the secretion of the adrenal medulla has long been known but it is now apparent that the secretion of the anti-diuretic gonadotrophic and adrenocorticotrophic hormones from the pituitary gland may be influenced by emotional states." He calls to attention the fact that in 1932, LeGros Clarke pointed out the importance of the fiber tracts uniting the cortex of the frontal lobe and the dorsomedial thalamic nucleus, and the fibers which connect this nucleus with the hypothalamus. He suggests that this anatomical system links up a dualism of psychic life, the hypothalamus concerned with the internal environment and the emotions, and the thalamus concerned with stimuli arising from the external environment. He states further that the operation of frontal lobotomy again focuses attention upon this tract, and he cites instances in which after lobotomy there was a marked change in endocrine activity.

From the trend of events in the last few years, we may logically

conclude that the divergent groups which have been off in diverse directions, seeing only one aspect of the problem according to their particular bias, may be nearer together than they think. Perhaps in the not too distant future, endocrinologists, psychoanalysts, neurologists, psychiatrists, chemists and neurosurgeons will "lie down together." They may even notice a kinship with Hippocrates, Aristotle, and Thomas Aquinas, and their dissertations upon humors. While we probably can never aspire to that felicitous state described in *Alice in Wonderland*, where everybody has won and all shall have prizes, it will not be altogether strange to see so many signs of agreement among the various disciplines. Certainly it is obvious that man functions as a unit, and that the major differences of opinion as to the manner of his functioning seem to relate to the emphasis which every group of specialists has put upon the particular aspects of the problem of interest to it.

Although the office of Ministry to the Mind Diseased has been sought by many candidates through the years, the office, like many others in the realm of Human Affairs, can be filled only by those whose philosophy and practice give impartial and proportionate representation to the entire body politic. This means that hormones participate in due ratio with sociology, economics and physiology, in the good government of the human emotions.

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MONTHLY PANEL MEETINGS ON THERAPEUTICS FOR THE GENERAL PHYSICIAN — 1953-1954*

Meetings held at the Academy 4:30 P.M. in Room 20

NOVEMBER 6, 1953

Subject: *CURRENT CONCEPTS IN THE MANAGEMENT OF FUNCTIONAL GASTROINTESTINAL DISORDERS*

Moderator: LAWRENCE S. KUBIE—Clinical Professor of Psychiatry, Yale University Medical School, New Haven, Connecticut

Panel Members: THOMAS P. ALMY—Associate Professor of Neoplastic Diseases (Medicine), Cornell University Medical College; Associate Attending Physician, New York Hospital

ROBERT HIATT—Instructor in Surgery, College of Physicians and Surgeons, Columbia University

GEORGE B. KOELLE—Professor of Pharmacology, Graduate School of Medicine, University of Pennsylvania

SYDNEY MARGOLIN—Associate Attending Psychiatrist, The Mount Sinai Hospital, New York

DECEMBER 4, 1953

Subject: *CURRENT CONCEPTS IN THE MANAGEMENT OF ASTHMA, EMPHYSEMA AND CHRONIC PULMONARY INFECTIONS*

Moderator: DICKINSON W. RICHARDS—Director and Visiting Physician, First (Columbia) Medical Division Bellevue Hospital; Lambert Professor of Medicine, College of Physicians and Surgeons, Columbia University

Panel Members: JULIUS H. COMROE, JR.—Professor of Physiology and Pharmacology, Graduate School of Medicine, University of Pennsylvania

ANDRE COURNAND—Professor of Medicine, Columbia University, College of Physicians and Surgeons; Director, Cardio-Pulmonary Laboratory (Columbia University Division) Bellevue Hospital

MORTON GALDSTON—Assistant Professor of Clinical Medicine, New York University College of Medicine

WILLIAM B. SHERMAN—Associate Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University; Attending Physician, Roosevelt Hospital

* A complete listing of Panel Members for the remaining meetings, will appear at a later date.

THE DIAGNOSIS AND THERAPY OF MYCOTIC INFECTIONS*

The A. Walter Suiter Memorial Lecture

DAVID T. SMITH

Duke University School of Medicine, Durham, North Carolina

THE mycotic and viral infections have acquired a position of relatively greater importance since most of the diseases caused by bacteria have been brought under control by preventive measures or by sulfonamide and antibiotic therapy. Indeed, certain types of mycotic infections have become more prevalent and more virulent following prolonged therapy with the newer antibiotics.[1]

Unlike most bacterial and viral infectious diseases the systemic mycotic infections are not transmitted directly from patient to patient; consequently one would not expect to see epidemics caused by fungi.[2-4] In most instances the mycotic infections are endemic and sporadic but true epidemics of sporotrichosis, coccidioidomycosis and histoplasmosis do occur when groups of nonimmune individuals are exposed to an environment containing large amounts of the saprophytic form of the fungus. More than a thousand cases of sporotrichosis developed in the gold mines of South Africa when the timbers in the mine became infected with Sporotrichum Schenckii.[5] Epidemics of coccidioidomycosis occurred when companies of nonimmune soldiers from the East marched in the dust of certain Southwestern deserts.[6, 7] Epidemics of histoplasmosis have occurred following the exposure of groups of nonimmune individuals to pigeon manure,[8a] chicken manure, bat manure in caves[9] and to the dust of unused silos.[10]

The frequency of subclinical infections with fungi may equal or even exceed that observed with tuberculosis and certain viral infections. This has been demonstrated by the studies of Kessel,[11] Aronson[12, 13] and C. E. Smith for coccidioidomycosis[14, 15] and those of Christie and Peter-

* Presented, by invitation, at the Stated Meeting of The New York Academy of Medicine, November 6, 1952.
Manuscript received November, 1952.

son,[16] Palmer[17, 18] and Furcolow[19] for histoplasmosis. These investigators prepared coccidioidin and histoplasmin from cultures grown in a synthetic medium originally designed for the production of tuberculin. The delayed tuberculin type of allergic skin test is found after infection with these fungi. The tests are administered, read and interpreted in the same manner as the tuberculin test. There is a blastomycin,[20] analogous to coccidioidin and histoplasmin, and a Blastomyces vaccine[21] available for the testing of patients infected with Blastomyces but these antigens are not as reliable for survey skin testing as coccidioidin or histoplasmin. This is not the fault of the antigen but results from the fact that Blastomyces dermatitidis is not as good a sensitizer as Histoplasma capsulatum or Coccidioides immitis. Not more than 75 per cent of proven cases of blastomycosis give positive allergic skin tests and only the occasional subclinical infection can be detected by a blastomycin skin test.

A Nocardia protein analogous to the tuberculoprotein PPD has been prepared from Nocardia asteroides.[22] This is a specific antigen which shows no cross reaction with tuberculin when tested on guinea pigs infected with tubercle bacilli. This nocardin has not been used on patients or in survey studies. We have demonstrated, in our clinic, positive tuberculin-like reaction to autogenous vaccines prepared from patients suffering from moniliasis, sporotrichosis, cryptococcosis, geotrichosis and aspergillosis. Not all proven cases give positive skin tests and the degree of reaction resembles that found in blastomycosis rather than the more severe reaction noted in coccidioidomycosis and histoplasmosis. Survey skin tests should be made with nocardin, sporotrichin and extracts or vaccines from the other systemic fungi but it is unlikely that they will be as efficient in detecting subclinical infections as coccidioidin and histoplasmin.

Endogenous and Exogenous Mycoses

The epidemiology of each specific mycosis is conditioned by the primary source of the organism. When the fungus is carried by man, in a manner analogous to pneumococci and meningococci, the mycoses are found in all age groups and affect females almost as frequently as males. Actinomyces bovis is carried in the gums about the teeth of apparently normal individuals[23-26] although it is found more often in larger numbers in the mouths of individuals with poor dental hygiene.

TABLE I—EXOGENOUS AND ENDOGENOUS MYCOSES

Exogenous	*Endogenous*	*Exogenous or Endogenous*
1—Histoplasmosis	10—Actinomycosis	13—Cryptococcosis
2—Coccidioidomycosis	11—Moniliasis	14—Aspergillosis
3—North American Blastomycosis	12—Geotrichosis	15—Penicillosis
4—South American Blastomycosis		16—Mucormycosis
5—Nocardiosis		
6—Sporotrichosis		
7—Chromoblastomycosis		
8—Mycetoma		
9—Rhinosporidiosis		

Monilia and various species of Geotrichum, Penicillium, Aspergillus and Mucor can be isolated from the saliva, skin, vagina and stools of apparently normal individuals.[27-29] Cryptococci have been isolated from apparently normal skin but also from the juice of certain fruits,[30] from the soil,[31] and from mastitis in cows.[32]

The endogenous fungi with the exception of Actinomyces bovis multiply rapidly and apparently become more virulent when the normal ecologican flora of the body are materially reduced or eliminated by prolonged therapy with the newer broad coverage antibiotics.[1] With the possible exception of cryptococcosis, the diseases which are classified in Table I as either endogenous or exogenous-endogenous also increase in number following antibiotic therapy.

The exogenous fungi (Table I) multiply and survive either in soil or on plant material (Table II). Nocardia asteroides, and related species, and Sporotrichum Schenckii are apparently rather evenly distributed throughout the world; consequently infections with these fungi are found everywhere. The remaining fungi of the exogenous type occur predominantly or exclusively in certain restricted geographic areas (Table III). The exogenous fungi may infect children and women but occur with greatest frequency in adult males who go about the fields and forests and come in contact with the natural source of the saprophytic form of the fungus.

TABLE II—NATURAL SOURCE OF EXOGENOUS FUNGI

Organism	*Isolated from*
Histoplasma capsulatum	Soil[66-69] Silo[70]
Coccidioides immitis	Soil[59]
Blastomyces dermatitidis	Soil suspected[42]
Blastomyces braziliensis	Vegetable material[42]
Nocardia asteroides	Soil[58]
Phialophora verrucosa	Wood pulp[71]
Sporotrichum Schenckii	Soil[73] Mine timbers[40]
Allescheria boydii	Soil[75]
Aspergillus fumigatus	Cereal grains, etc.[74]
Cryptococcus neoformans	Soil[31] Peach[30]
Rhinosporidosis	Stagnant water suspected[42]

TABLE III—GEOGRAPHICAL DISTRIBUTION

Mycoses	*Distribution*
1—Actinomycosis	World wide
2—Aspergillosis	World wide
3—Coccidioidomycosis	South Western U.S.A., Argentina
4—Chromoblastomycosis	Every continent except Asia
5—Cryptococcosis	World wide
6—Geotrichosis	World wide
7—Histoplasmosis	Central U.S.A. In specific areas over world
8—Moniliasis	World wide
9—Mucormycosis	World wide
10—Mycetoma	Tropical and Subtropical areas
11—Nocardiosis	World wide
12—North American Blastomycosis	South Eastern and Central U.S.A. and North America
13—Penicillosis	World wide
14—Rhinosporidiosis	Tropical and Subtropical areas, Southeastern United States
15—South American Blastomycosis	South America
16—Sporotrichosis	World wide

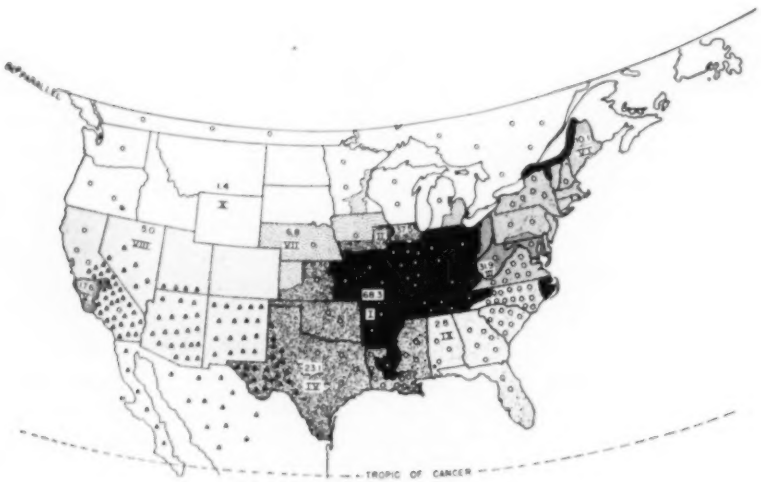

Figure 1—Distribution of histoplasmosis, blastomycosis and coccidioidomycosis in North America. The histoplasmosis areas are shown in black. The blastomycosis areas as circles and the coccidioidomycosis areas as triangles.

Geographic Distribution of Exogenous Fungi in the United States: Often a clue to the correct diagnosis in an obscure infection can be obtained by a careful history of the areas of residence for the previous five years. Most significant is the area of residence for two to three months before the onset of symptoms.

The exogenous fungi most frequently found in this country are Histoplasma capsulatum, Coccidioides immitis and Blastomyces dermatitidis. Figure 1 shows the geographic distribution of histoplasmosis as determined by the studies of Carroll E. Palmer.[18] The new area around Lake Champlain and along the St. Lawrence River was found by White[8b] and Guy,[33, 34] and the area in Northeastern North Carolina by Murphy.[35] It is probable that more intensive studies will reveal other small areas of high incidence outside the main area in the center of the country. It should be emphasized that this chart shows the incidence of subclinical infections as revealed by the histoplasmin test and not the number of clinical cases, although most clinical cases occur in natives of the endemic areas or in visitors to those areas.

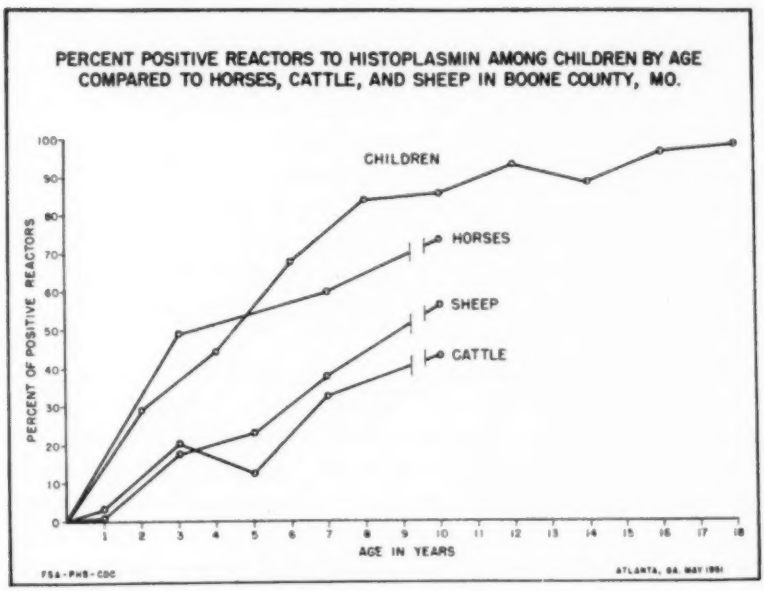

Figure 2—Rate at which sensitivity to histoplasmin is acquired in Boone County, Missouri, by children, horses, sheep and cattle. (From Menges, R. D. *C.D.C. Bull.* 10:8, May 1951. Reprinted by permission.)

The white circles which have been superimposed on the histoplasmin chart shown in Figure 1 represent the distribution of proven clinical cases of North American blastomycosis. It can be seen that the greatest concentration of cases occurs in the southeastern states, although almost as many cases develop in the Mississippi River valley. Isolated cases are found throughout the United States, on the Pacific coast and in both eastern and western Canada. There are about as many clinical cases of blastomycosis each year as histoplasmosis and presumably the subclinical cases of blastomycosis equal the subclinical cases of histoplasmosis but this cannot be demonstrated, since we lack a method for the detection of subclinical blastomycosis.

The triangles superimposed on the histoplasmin chart shown in Figure 1 represent the distribution of coccidioidomycosis cases. The greatest concentration of clinical and subclinical cases is found in the

semi-arid sandy areas in southwestern United States, although the disease extends on into Mexico and reappears in dry sandy areas in Argentina, South America.

Clinical Diagnosis of Mycotic Infections

A mycotic infection can be suspected from 1) the place of residence, 2) symptoms, 3) physical signs and 4) roentgenograms but is rarely diagnosed without supporting data from the laboratory. The initial symptoms are indistinguishable from those of an ordinary upper respiratory infection or a viral or rickettsial infection of the lungs. If the disease persists for several months the clinical picture begins to simulate tuberculosis or a neoplastic disease.

The Use of Skin Tests in Diagnosis: Histoplasmin, coccidioidin, blastomycin and tuberculin skin tests should be used in the study of patients suspected of having mycotic infection. These tests are useful often but also may be misleading. They should be administered and interpreted in a manner analogous to the tuberculin test. Certain points should be emphasized. The skin tests are negative in initial stages of the infection and some rapidly advancing cases, especially of histoplasmosis, progress to death without ever developing a positive skin test. Terminal cases of histoplasmosis, coccidioidomycosis and blastomycosis, like terminal cases of tuberculosis, frequently become anergic and give negative skin reactions. A positive reaction to a skin test, like a tuberculin test, means present or past infection.

There seems to be a small amount of a common antigen in Coccidioides immitis, Histoplasma capsulatum and Blastomyces dermatitidis and this results in some cross reaction in the skin tests.[20,36] For this reason histoplasmin, coccidioidin and blastomycin should always be administered simultaneously regardless of which mycosis is suspected. Only those patients with excessive sensitivity to coccidioidin, e.g., positive to 1:10,000 dilution, give a cross reaction with histoplasmin or blastomycin.[36,37] Cross reactions between histoplasmin and blastomycin are much more common, with the major cross being between histoplasmin and blastomycin. In our experience, individuals with marked positive skin tests to histoplasmin usually give reactions to blastomycin or standard Blastomyces vaccine which are from 25 to 50 per cent as large as the specific reaction to histoplasmin. Such an individual may give a larger reaction to blastomycin than some patients with proven blasto-

mycosis. Patients with large reactions to blastomycin may give smaller reactions to histoplasmin. The specific reaction is always larger when the three antigens are given simultaneously and no difficulty is encountered in interpretation.

The Use of the Complement Fixation Test in Diagnosis: The complement fixation test for blastomycosis was introduced by Martin in 1933.[38] The antigen was prepared from the pulverized bodies of the tissue phase of Blastomyces dermatitidis. C. E. Smith of California used coccidioidin for the antigen and perfected a complement fixation test for coccidioidomycosis.[15] The antigen used in the complement fixation test for histoplasmosis may be histoplasmin or the yeast phase of the organism.[39-41]

Complement fixing antibodies are not stimulated by subclinical infections or even mild clinical infections or, if present, are not in amounts sufficiently high to be detected by the methods now in use. Apparently a rather marked stimulation of the tissues is necessary to induce demonstrable amounts of complement fixing antibodies. A positive complement fixation test should be interpreted as evidence of active infection and unlike the skin test the titer continues to rise in terminal cases. Conversely the titer declines as the patient improves and disappears after recovery.

There is little, if any, cross complement fixation between the sera of patients with coccidioidomycosis and the histoplasma and blastomyces antigens. There is, however, a marked cross reaction between the sera of patients with active histoplasmosis and the blastomyces antigen. The cross reactions in the reverse direction are minimal. A patient with active histoplasmosis may give a higher titer of fixation with a blastomyces antigen than a proven case of blastomycosis may give with the same antigen. For these reasons sera should be run in parallel against both histoplasma and blastomyces antigens.[41] When this is done, no difficulties are encountered in interpretation.

The Isolation of Fungi: Actinomyces bovis is anaerobic and requires a rich medium for growth.[42] Fortunately all the other fungi which cause systemic infections in man are aerobic and will grow on a modified Sabouraud's medium which is a simple peptone agar of pH 5 to 6 which contains 4 per cent dextrose. The rate of growth varies with the type of fungus. Monilia, Aspergillus, Penicillium, Mucor and Geotrichum grow rapidly with the production of large colonies in four to five

days. Isolated colonies should be picked for subculture but the original tubes should be kept for at least thirty days. Cryptococcus neoformans and Sporotrichum Schenckii may appear after ten to fourteen days and Histoplasma capsulatum, Coccidioides immitis and Blastomyces dermatitidis after twenty days. It is most important that the tubes showing an early growth of Monilia are not discarded. We have found Monilia as a secondary invader in cases of blastomycosis, cryptococcosis, histoplasmosis and coccidioidomycosis. The saprophytic form of Histoplasma capsulatum, Coccidioides immitis and Blastomyces dermatitidis give a growth which resembles a tuft of white cotton. Before the development of characteristic spores these fungi cannot be distinguished from each other or from certain nonpathogenic fungi which may appear on the medium.

The yeast-like tissue phase of Blastomyces dermatitidis grows readily in five to seven days when inoculated on blood agar and incubated at 37°C.;[42] and the tissue phase of Sporotrichum Schenckii grows well on the cystine medium designed for the cultivation of Pastuerella tularensis.[43] Nocardia grows equally well on dextrose agar, blood agar or the special media used for growing Mycobacterium tuberculosis but unlike tubercle bacilli they are destroyed by the various types of concentration procedures commonly used to eliminate contaminants from tuberculous material. The tissue phase of Histoplasma capsulatum may grow on blood agar or in special fluid media[39] when incubated at 37°C. Sometimes on these media the growth starts as the tissue phase and changes over to the saprophytic mold-like phase even when growing at 37°C. The spherule endospore tissue phase of Coccidioides immitis has been grown occasionally on artificial media[44a] but most strains grow only in the saprophytic phase even on rich media at 37°C. However, an abundant growth of the spherule-endospore form can be obtained by inoculating the material into the yolk sac of embryonated eggs.[44b]

Various modifications of the basic media have been advocated with the object of making the media more selective for fungi. In Littman's modification gentian violet is added to suppress bacterial growth.[45] This modification is definitely superior to the usual Sabouraud's medium for the isolation of the dermatophytes from skin, hair and nails and for the isolation of fungi from stools. It has definite limitations, however, since the gentian violet inhibits the growth of Actinomyces bovis, Nocardia asteroides, Candida albicans and partially inhibits the growth of

Histoplasma capsulatum. The addition of 1000 units of penicillin and 200 micrograms of streptomycin to blood agar medium efficiently eliminates bacteria without affecting the yeast-like and mold-like fungi.[46] But the antibiotics prevent the growth of Actinomyces bovis and Nocardia asteroides and related species of Nocardia.

Direct Microscopic Examination for Fungi: When the organisms are present in abundance, a direct microscopic examination of such specimens as pus, sputum, urine, tissue or spinal fluid may reveal the characteristic fungus. Unstained wet-mount preparations are superior to stained preparations except where Histoplasma capsulatum and Nocardia asteroides are suspected. Giemsa's stain may reveal Histoplasma capsulatum in the cytoplasm of large mononuclear cells from the bone marrow, lymph nodes or sputum. Nocardia asteroides is partially acid fast and is demonstrated most easily in smears stained with the standard Ziehl-Neelsen method used for the demonstration of tubercle bacilli. Over-decolorization with acid alcohol should be avoided. The organisms resemble tubercle bacilli in width but are often longer; many of them show side branches.

When the organisms are few in number they are difficult to detect by direct examination and even more difficult to differentiate from artifacts which resemble fungi. In all instances the direct examination whether postive or negative should be confirmed by cultures. However, the diagnosis of actinomycosis by the demonstration of the typical "sulphur granule" in wet-mounts, if supplemented by a gram stain of the granule, is more reliable than when cultures are used from material containing secondary bacteria.

The Examination of Material Removed by Biopsy: Diagnosis by biopsy is more rapid than by culture and quite as reliable provided the typical organisms are present in the section. The tissue reaction alone does not permit a definite diagnosis. The new periodic acid staining technique of McManus[47] is definitely superior to staining by the hematoxylin-eosin or Giemsa's methods. Occasionally organisms are found in tissue by the McManus method when cultures from the same tissue fail to yield a growth, but in general the cultural methods are more reliable than biopsy and staining. It is most important that cultures be made of material suspected of containing Sporotrichum Schenckii since these organisms are rarely seen in tissue biopsies from man but usually grow readily in culture.

Therapy

The general therapy for the mycotic infection is the same as that for tuberculosis, namely bed rest and good food. But isolated lesions which do not respond readily to therapy should be resected by surgeons. Specific therapy may be directed 1) against the granulation tissue which harbors the organisms, 2) against the organism itself or 3) in support of the specific immune mechanism of the patient. In some instances two or even all three of these methods of therapy are applied simultaneously or in succession.

Treatment of Actinomycosis: Actinomyces bovis is about as susceptible to the sulfonamides and penicillin[48] as most gram-positive cocci but the patients require months of treatment because the organisms are hidden away in relatively avascular granulation tissue or in encapsulated abscesses. The administration of a saturated solution of potassium iodide in gradually increasing doses facilitates the absorption of the granulation tissue and favors the penetration of the infected areas by sulfonamides or penicillin. In advanced cases surgical drainage and even surgical excision may be required but medical therapy with sulfonamides, penicillin and iodide should be continued for six months postoperatively to prevent relapses.

Treatment of Nocardiosis: Nocardia asteroides, in contrast to Actinomyces bovis is quite resistant to penicillin therapy and relatively resistant to the newer antibiotics.[49] Sulfonamides, especially sulfadiazine, is the most effective drug for nocardiosis.[50-52] Recovery requires months of therapy because of the nature of the granulation tissue. Iodides should be administered concurrently with the sulfonamides and surgery employed when indicated.

Treatment of Sporotrichosis: Iodides gained their reputation as a specific for mycotic infections because of their dramatic curative effect in sporotrichosis. The response, however, is relatively slow and the drug should be continued for at least three months after the disappearance of the lesions and symptoms. Some few patients develop an excessive sensitivity to the products of the fungus which can be demonstrated by a skin test made with a heat killed vaccine prepared from the tissue phase growth of Sporotrichum Schenckii. Such patients may not make a complete recovery with iodides until desensitized with the vaccine. Stilbamidine inhibits the growth of Sporotrichum Schenckii on artificial

media in quite low concentration and might prove to be effective in patients who are responding slowly to iodides.

Treatment of Blastomycosis: The therapy of cutaneous blastomycosis is somewhat different from that of pulmonary and systemic blastomycosis. Cutaneous blastomycosis without allergy, as demonstrated by a negative skin test to blastomycin or Blastomyces vaccine, usually heals in a period of months after therapy with iodides and x-rays. Patients with positive skin tests often do not respond to their iodides or x-rays until they are desensitized. After partial desensitization they heal as readily and as completely as those which were not originally hypersensitive.[21, 53]

Pulmonary and systemic cases of blastomycosis show little if any improvement after x-ray therapy. The results of vaccines and iodide vary with the immunologic status of the patient.[53] Patients in good physical condition, whose tissues have made some response to the invading organism as shown by the presence of complement fixing antibodies, usually respond to iodide therapy. The improvement is slow and one to three years of iodide therapy may be required. Patients with disseminated systemic blastomycosis who have a relatively high titer of complement fixing antibodies and negative skin tests are anergic and usually die in two to three months. This group of patients is not helped by either vaccines or iodides. The patients who have positive skin tests, with or without accompanying complement fixing antibodies, usually fail to improve with iodides and their disease may become rapidly progressive following the use of iodides. However, if such patients are partially desensitized with Blastomyces vaccine and then treated with iodides they usually improve as rapidly as the patients who were not originally hypersensitive.[53, 54]

Iodides should not be administered too early to patients with pulmonary and systemic blastomycosis who have developed no immunity to the organisms since the iodides force a resolution of the granulation tissue, liberate the organism and induce dissemination.[53] Patients in this group have negative skin tests and negative complement fixation tests. They should be immunized with the Blastomyces vaccine; repeated courses of vaccine are given until they show either a small positive skin reaction or complement fixing antibodies or both. After this indirect evidence of immunity is demonstrated they respond satisfactorily to iodide therapy in most instances.

Stilbamidine Therapy for Blastomycosis: Stilbamidine is apparently a specific drug for blastomycosis. Introduced and used for years in the treatment of visceral leishmaniasis or kala-azar it was employed in the treatment of blastomycosis by Schoenbach and his associates in 1950.[55] We do not use stilbamidine in the treatment of cutaneous blastomycosis unless the patient fails to respond to the therapy outlined above. However, it is now our first choice in all cases of pulmonary and systemic blastomycosis regardless of the immunological status of the patient. Stilbamidine is not a harmless drug and should be administered with care. Unlike the sulfonamides and antibiotics, the drug accumulates in the tissues and remains for several years. Fresh solutions of the drug, diluted in 100 to 300 ml. of physiological saline, should be dripped into a vein over a period of one to three hours. Schoenbach gave daily injections of 50 to 150 mg. for a period of ten days, allowing a rest period of ten to twenty days and repeated the course as often as necessary. We have given one continuous period of treatment for thirty days. Progressive improvement has occurred in our cases for two to three months after a single period of thirty days of treatment. A new course is not indicated unless the organism reappears and the patient develops new lesions. This is a new treatment and its dangers and limitations have not been evaluated. It is known that evidence of injury to the sensory root of the 5th nerve may appear three to four months after the drug has been discontinued.

Treatment of South American Blastomycosis: South American blastomycosis responds well to intensive therapy with sulfadiazine[56] but the patient may relapse and die when the drug is discontinued. Stilbamidine should be tried as a therapy for this mycosis.

Treatment of Chromoblastomycosis: Chromoblastomycosis responds slowly to months or years of therapy with iodides.[42] The danger to life is negligible and the affected limb should not be amputated. There is suggestive evidence from laboratory studies that stilbamidine might be effective in this mycosis.

Treatment of Histoplasmosis: Subclinical and mild clinical infections with Histoplasma capsulatum require no specific therapy. An occasional patient with a generalized infection, including an enlargement of the spleen, recovers spontaneously, leaving as a residue a miliary-like calcification of the lungs and spleen. Most patients with systemic histoplasmosis die of their infection in one to nine months. A few pa-

tients with systemic histoplasmosis have recovered following intensive therapy with ethyl vanillate.[57] This drug is difficult to administer and obviously is not comparable in its effects to stilbamidine in blastomycosis.

Patients in reasonably good physical condition who have indolent lesions and excessive sensitivity as shown by the histoplasmin skin test might recover following desensitization and iodide therapy. Isolated re-infection types of lesions which do not respond properly to therapy should be excised.

Treatment of Coccidioidomycosis: Patients with subclinical and mild clinical infections with Coccidioides immitis recover without specific therapy. Often residual, thin walled cavities develop in the clinical cases. If these do not heal in three to six months they should be resected by the thoracic surgeon. Most of the patients with disseminated lesions die in three months to one year but some recover spontaneously.[42] If the patient with a disseminated infection has a marked positive reaction to coccidioidin recovery may be hastened by desensitization with this product. Actidione[58] and prodigiosin[59] have been used with some success but these antibiotics themselves are quite toxic.

Treatment of Cryptococcosis: The primary lesions in cryptococcosis (torulosis) may be in the subcutaneous tissue or the skin but occur most often in the lungs. The pulmonary lesions may be quite small and undetectable clinically or by x-ray. This organism has a great predilection for the brain and meninges and often the primary symptoms suggest tuberculous meningitis, encephalitis or neoplasm. In acute cases, the organisms multiply in the tissues without cellular or immunologic reactions. Agglutination, complement fixation and skin tests are usually negative. A few patients have recovered following treatment with sulfadiazine[60] and a few after actidione therapy.[61] Some patients with skin, pulmonary or bone lesions or with chronic recurrent meningeal symptoms do give evidence of immunological response by having a positive agglutinin reaction and/or a positive skin test to their own organism. The patient's own organism must be used for the preparation of a vaccine since there are at least three immunological types of Cryptococcus neoformans.[62] We have obtained good results in patients with skin, pulmonary and bone cryptococcosis with desensitization, sulfadiazine and iodides when agglutinins and positive skin tests were present.

Treatment of Maduromycosis: Maduromycosis may be caused by various species of Nocardia, Actinomyces bovis or a large group of hyphomycetes.[63] The therapy depends upon the type of fungus. Nocardia responds best to sulfonamides, Actinomyces bovis best to sulfonamides or penicillin while the hyphomycetes respond to neither. Stilbamidine should be tried for organisms of the hyphomyces type. If the patient does not respond to medical treatment in a few weeks the foot or leg should be amputated.

Treatment of Rhinosporidiosis: There is no known effective medical treatment for this mycosis. The lesions should be excised.[64, 65]

Treatment of Endogenous Fungus Infections: Moniliasis, aspergillosis, penicilliosis, mucormycosis and geotrichosis[2, 42] are difficult to evaluate. The fungi causing these diseases are those described above. They may occur as contaminants in cultures; they are often secondary invaders and only occasionally the primary and sole cause of the lesion. We prepare autogenous vaccines from the culture of the patient and test for sensitivity with a skin test. If the patient is hypersensitive we desensitize with the vaccine and then administer iodides.

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PSYCHOANALYSIS AND THE CYCLES OF LIFE*

PHYLLIS GREENACRE

Professor of Clinical Psychiatry, Cornell University Medical College

SIGMUND FREUD in whose honor we gather tonight was born ninety-seven years ago on May 6th, 1856. Thus it is still not yet one hundred years since his birth, and approximately sixty years since the first publications which marked the starting point of the long unfolding of his research into psychical processes and the development of that branch of science to which he gave the name *psychoanalysis*. Although its origin was clinical and arose from the needs of a young physician to understand and help his neurotic patients, its scientific searchlight has gone far beyond the demands of therapy alone. Writing in 1929, Freud stated "the future will probably attribute far greater importance to psychoanalysis as the science of the unconscious than as a therapeutic procedure."

It is my hope and my ambition tonight to present in this brief lecture a vista of the field of psychoanalysis from a natural history point of view and in terms not of the professional psychoanalyst,—be he clinician or research man,—but of the informed layman, the journalist, if you will, for this is a lecture for the public and not for a seminar.

My subject is "Psychoanalysis and the Cycles of Life." By a Cycle of Life I mean a period in which a certain round of events or phenomena is completed. In the biological cycles of life it is understood that the completed round of events or phenomena is in a fundamental sense predetermined, the pattern of their unfolding is somehow already laid down from the beginning, and only the secondary manifestations, the individual traceries upon the basic designs are appreciably variable, though important. It will be my effort then to put before you some of the fundamental discoveries of psychoanalysis regarding the cycles of life of the human being in their psychical manifestations and especially the significance in these of the interplay of the unconscious and the conscious forces in our activity.

I would think, in a pictorial simile, of the individual life span as like

* The Freud Anniversary Lecture of the New York Psychoanalytic Institute. Delivered at The New York Academy of Medicine, May 6, 1953. From The New York Hospital and the Department of Psychiatry, Cornell University Medical College.

a great bridge of many arches, extending from the first fertilized egg cell of its inception out through time and space, until it comes to an end in death. It increases in physical size and strength most rapidly during the early part of its course, remains relatively stationary in structural size for the middle and greater part of its span, and then gradually is disrupted until it finally becomes no longer usable. But the constituent arches, or secondary cycles, of this miraculous life span are not identified and regularly placed subdivisions,—like so many evenly rhythmed decades, such as a mechanical engineer might contrive. Each has, rather, its own organic length and proportions, not changed very basically by differences in outer conditions, but recurring with the same regular unevennesses in each new life's construction. Actually such a simile cannot be *quite* sound, for one cannot accurately compare something of inanimate structure to an organically living structure,—and the bridge of life does change,—is not so completely fixed as my picture would indicate, but evolves as all biological formations do,—but the process of change in structural relationships is so slow that for practical purposes we may use this diagrammatic representation.

Most of us accept the principles of biological evolution and see in the development of any individual creature some recapitulation of the history of its biological ancestors. They may be observed most strikingly in that intensely compressed historical review, in intrauterine life; not only because the kaleidoscope of anatomical development here moves so rapidly in its approximation of a repetition of biological history, but also because intrauterine life is—relatively speaking—more protected and evenly sustained, i.e., freer from encroaching environmental stimulations, which produce immediate responses blending with and masking the underlying biological developmental patterns or rhythms. It is our belief, however, that these fundamental phases or cycles of development throughout the entire life underly certain nodal problems of our psychological and emotional life: they form the central points or cores of strength and of strain which influence both psychic and physical struggles. They are then the common growth axes which under certain conditions produce neurotic developments whether these are expressed largely in psychic or in somatic forms.

Two main cables of life may be described in the aggressive and the sexual instincts of man,—which were called by Freud the Death and the Life Instincts. It may at first seem paradoxical to think of a *death*

instinct. This conception is based essentially on the question of whether or not death is a natural process (excluding death from violence, accident, or parasitic invasion), a condition the expectation of which is laid down from the very beginning and toward which life inevitably moves. It is a conception which arouses much questioning and is not readily accepted, possibly partly due to our resistances to the thought of death itself and to our powerful conceits concerning our abilities to control our own fate. Looked at from another angle, we may see that growth itself in its mighty expansiveness would seem to lead inevitably by its very force to an ultimate destruction of the organism. Yet the instinct of aggression (growth-death) does not ordinarily exist alone but is combined with the also powerful sexual instinct. It must be emphasized that by the sexual instinct is meant not only the strong specialized drive which brings people together in genital union, but rather that total mass of physical and emotional attractions between human beings causing them to seek out one another in any number of different forms of contact: the demand for relationship with other human beings and the abhorrence of loneliness. Indeed it seems that the pull of the sexual instinct deflects some of the destructiveness of untrammelled growth and aggressions, utilizing them rather in the interest of pleasure, satisfaction, and reproduction,—leading then to a biological eternal life. In this way the force of the death instinct does temporary service to individual life and the continuation of the species, but ultimately gains the ascendancy in the death of the individual.

Perhaps the fact that isolated and emotionally abandoned infants, unwarmed by interested human contact, tend to sicken and to die early even when given adequate food and mechanical but impersonal care, is an indication of the power of the death instinct when untamed by combination with the sexual instinct.

In the process of evolution man rises to an upright position, and develops a more complicated brain and central nervous system than other animals. He develops not only the intelligence of some other animal species based on the perceptual use of experience plus an ability to vary behavior by this experience rather than remain confined in the rigid but complex behavior on a pure instinct basis, such as is seen in the highly complicated social lives of some insects. Over and above this form of intelligence, he develops the capacity for *reason* and *imagination*. He has an ability for conceptual thinking, and symbolization, a capacity to ex-

periment with general ideas and to form variations not by chance alone, but by definite selection. He develops his voice, not merely as a sexual call or in another expression of emotion, but in that complex and enormously economical form of language, permitting contact and communication with myriad subtleties and adaptations. All in all, man's development of intellect and reasoning permits him a greater mastery of behavior than is true in lower animals. In that he is no longer so dependent on purely instinctual patterns of action or on automatic reflex reactions to adventitious external stimuli, he becomes at once both more controlled and more nearly a free agent, capable of choice and judgment. "The inner aspects of behavior—experimenting, learning, thinking, feeling and willing, come to count more and more."*

But man, with all this marvellous development of intellect, imagination and reasoning is still an animal, carrying the force of his animal heritage with him,—a fact which he, in his pride, sometimes forgets or turns away from. And whenever he ignores this part of himself and sees himself not as the total animal-man, which he is, with biologically driven pressures as well as cerebral controls, he becomes increasingly vulnerable to internal tensions and strains which may on occasion affect the harmony of his life and activity.

Shakespeare, in "As You Like It," puts the ages of life this way:

> "One man in his time plays many parts,
> His acts being seven ages. At first the infant,
> Mewling and puking in the nurse's arms.
> And then the whining school boy, with his satchel
> And shining morning face, creeping like snail
> Unwillingly to school. And then the lover
> Sighing like furnace, with a woeful ballad
> Made to his mistress' eyebrow. Then a soldier
> Full of strange oaths and bearded like the pard,
> Jealous in honour, sudden and quick in quarrel,
> Seeking the bubble reputation
> Even in the cannon's mouth. And then the justice
> In fair round belly with good capon lined,
> With eyes severe and beard of formal cut,
> Full of wise saws and modern instances;
> And so he plays his part. The sixth age shifts
> Into the lean and slipper'd pantaloon,
> With spectacles on nose and pouch on side,
> His youthful hose, well saved, a world too wide
> For his shrunk shank; and his big manly voice,
> Turning again toward childish treble, pipes
> And whistles in his sound. Last scene of all,
> Is second childishness and mere oblivion,
> Sans teeth, sans eyes, sans taste, sans everything."

* Thomson, J. A. *Outline of Science*. New York, Putnam, 1922, vol. 1.

We would not follow exactly the ages of man, so unsurpassingly and tersely described by Shakespeare, although in a general way the biological subdivisions are similar. We, too, would speak of seven periods, or seven cycles in the human life which have characteristic and specific impact on man's psychobiological development: 1) the prenatal period, —i.e., period from conception until birth; 2) the period of infancy extending roughly from the time of birth until about the age of five; 3) the period of childhood from five until puberty—approximately at the age of twelve; 4) the period from puberty until maturity—i.e., adolescence, roughly twelve to twenty-one; 5) the period of maturity, which comprises the span of active fulfillment in family and personal emotional ties, and in work achievement; 6) the era of involution, which we may place roughly as from the late forties into the sixties with great individual variations; and finally, 7) the period of old age.

It will be noted that the farther from conception we get, the greater are the individual variations in lengths of the cycles and the lesser is the rate of growth. Thus the period of prenatal development is quite regularly nine months long, and when birth does occur before this nine month period has been completed, the baby is not yet really in a developmental stage to be born,—from the infant's angle such premature birth is an accident, rather than a developmental achievement. This first, or intrauterine, cycle of life differs from all later ones in that there is no fetal psyche or emotional life per se. Further, in the fetus, completely surrounded as it is by the mother and completely in contact with her, the most amazing speed of growth occurs,—with so astounding an increase in size and weight, that there would be a veritable explosion if this force of growth were independent of the organizational pulls laid down by the already determined history of the species,—an organization which prepares the fetus for separation from the mother and the beginning of the long journey of life, often spoken of as one of "independent" life. This independence is, however, illusory, for with the gradual relinquishing of first the physical and then the special emotional ties to the mother, there is, inevitably, a reaching out emotionally to other human beings. There is, it seems, no real independence but death.

It was the discovery of Freud that the emotional patterns of any individual adult life are but repetitions (somewhat changed by growth) of earlier patterns, the main outlines of which have been laid down by the experiences of the first years,—especially in the period of infancy

up to the age of five to six. We can accept quite readily the idea that certain physical experiences may affect our entire later physical well-being, either protecting us somewhat or predisposing us by creating special areas of weakness and susceptibility, but it is much harder to realize that the emotional experiences of the first years leave permanent imprints, whose force is felt in the very organization of the growing psyche creating definite tendencies to action even though the conscious memory of original experiences is lost. Indeed, we may say that the memory is retained and expressed in its very effect on the psychic organization,—rather than being subject to conscious recall. No experience is totally lost to the individual, and insofar as it exists only in the organization of the psyche and not in the forefront of our awareness, it is unconscious. It then exerts an organizational pressure, not specifically challenged by judgment, choice or reason. Insofar as it remains conscious or can be made conscious, it may be more clearly possessed and appreciated by us. In no period of life as much as in that of infancy up to the age of five, are so many experiences officially "forgotten," i.e., unconscious. Freud's discovery of the importance of this early period was extremely upsetting to the more generally accepted idea: that what the child does not remember is permanently gone and cannot possibly have any effect upon the later life. Indeed, it used often to be thought that it was much better if suffering occurred earlier rather than later in childhood on the basis that the earlier such bad experiences occurred, the more they were disposed of through being forgotten.

In this first period then of infancy, the rate of physical growth, compared with that of later life, remains exceedingly high, though not at any time at all approaching the rate of weight and size increase which has been true before birth. Certain organs or systems of organs develop more rapidly than others. These variations in developmental processes depend not so much on the individual needs of any special child, and not even entirely upon the common needs for most children at any given age, but predominantly upon the historical needs of the whole ancestry of these present children, which have already become knit into the regular organizational pattern of the given period of life. For biological development, like much of human law, in its organization rarely keeps abreast of the current demands, but enjoys some degree of conservative lag, and is constantly being jostled into new variations by rebellious individuals, who sometimes produce improvement and sometimes only strain.

To return to the situation of the infant under five, he undergoes a prodigious functional development and makes rather amazing strides toward his quasi-autonomous later life. Within the first year to eighteen months he has generally withdrawn from the exclusiveness of his partnership with his mother; his muscles have developed to an extent that he first sits up and then rises to his feet and walks; he has erupted a fair mouthful of teeth and is no longer content only to suck but must chew also. He has developed his crying and his laughing into specialized forms of communication and has in most instances begun to talk. It is impossible to enumerate in this short space, much less to describe, the enormous functional development of the infant in these early months. Most important, however, is the fact that in the increasing and inevitable breakdown of the mother-infant partnership through the very laws of growth, the infant becomes definitely aware of others as well as the mother or series of mothers who feed and tend him. He differentiates one individual from another and has an increasing awareness of himself too, as one among the group. The beginning of this individuation and awarenesses probably occurs largely through body sensations,—changing stimulations from the outer world of things and people as well as from the sensations arising from within his own body,—stimulations and sensations which delimit the sense of the body itself and contribute to pleasurable or unpleasurable awarenesses of the self and of others. While the first attachment has been to the mother, largely on an alimentary-and-olfactory or skin-and-body warmth contact with her, these primitive infantile love pleasures are somewhat sacrificed or crowded into a less conspicuous area by the very maturational processes going on within the body. Reliance on the mother as the source of body comfort and pleasant relaxed satiety gives way to a greater development of pleasure in the functioning of the body itself and gradually in the comparative awareness of other bodies as well, with imitativeness and rivalry gradually offering spurs to effort. Mastery of speech, walking, coordinated movement—in which the special senses play a conspicuous part—and finally the relatively secure control of excretory functions, all furnish their portion of gratification,—satisfactions which, arising largely from bodily activities, still are generally not experienced fully in solitude. In their very exercise they contribute to the communication and relationship with others.

The development of a sense of time and space is an extremely important product of maturation,—dependent perhaps upon the increasingly

strong awareness of inner rhythms of the body,—as in hunger, sleep and excretory needs, but also in the rising to an upright position with a new orientation to space, marked further by that combined appreciation of time and space which is a regular accompaniment of walking. Naturally this too is dependent upon development of vision and hearing as well as upon the increasing muscular strength and neuromuscular maturity. It may be important, however, to recognize that with the awareness of time and space comes the early appreciation that one thing may definitely and regularly follow another,—the very dawn of both reason and morals, with this primitive sense of cause and effect. Memory, not only as recognition but gradually as fantasy and anticipation, is a corollary.

It may be well next to mention the further development of the sexual love life of this infantile stage, the recognition of the existence of which has offended so many. Soon after birth there is some increased development of the special organs, assigned to the later pleasures and responsibilities of sexual functioning. While the genital organs show from the first some capacity for stimulation and response, these early responses seem to serve a somewhat different function from the fuller more sustained awareness and response of which the infant is capable at about the age of four or five. It is important, however, that this sexual awareness which occurs quite regularly at this period is not merely an isolated and meaningless phenomenon, but is actually associated with feelings first of self-awareness and then of ambitious tenderness, generally toward the parent of the opposite sex. Whereas the earlier relationship has been one of oral gratification (dependence on being fed) or of body contact pleasure with one or both parents, the occurrence of some miniature sexual love toward the appropriate parent—and who else is there so uniformly at hand to be the recipient—seems to arise rather regularly, dependent upon three conditions: 1) after there has been sufficient body awareness so that the child actually realizes that there are two sexes and is aware to which sex he belongs (a stage of body sophistication generally attained at about the age of three); 2) sufficient maturing of the nervous system to consolidate the sensory susceptibility of these special genital parts of the body; and 3) the presence of an appropriate and interested parent to be the recipient of these infantile longings. Major variations in any one of these conditions—and the third is likely to be the most variable—will naturally somewhat impede or distort the development of this regular progression of affairs, but under most circum-

stances it is part of and the last major event of the second cycle of life. Naturally the child's love affair at this time cannot be compared to an adult love affair,—to which, however, it is a precursor. The full exercise of sexual functioning is not yet possible and the little one's small-scale play for the desired parent and rivalry with the parent of the same sex is doomed in most cases to disappointment and failure. It is doomed not only by the attitude of the parents, but by the very non-cooperation of the physical development in the next stage or cycle of life. Still, the intensity with which this attachment develops, and especially the nature of its termination by fear or frustration,—or the failure of the latter, sometimes through overly strong reciprocation by the parent,—all these exert a powerful influence upon all versions of sexual awareness and attraction experienced in later years.

Whether or not this early period of susceptibility to sexual attraction represents an earlier biological and social stage when mating did occur within the family and under developmental conditions which, according to our present standards are, to say the least, immature, must remain somewhat a matter of speculation. But that such a stage of rise of sexual interest directed toward another person and experienced not merely as a pleasure stimulus of the own body occurs, as part of the predetermined cyclic development of life, is evident from the careful life studies in which the unconscious pressures as well as the conscious motives may be investigated.

If so much time has been spent upon this expanding infantile cycle, it is because this period furnishes to an extraordinary degree the basic models on which later important emotional relationships will be fashioned. Many events which are considered by the adult individual either to be the result of his own free choice or on the other hand to have resulted from the merest current chance may be found on investigation to have important elements determined by these early events which the adult has long since "forgotten" and of which he is therefore unconscious. Not only are the unique configurations of early emotional relationships sometimes amazingly repeated, but many character attitudes have their inception then, not only by direct repetition of tendencies established early but also by counter attitudes directed against early tensions and suffering. These may be effective, or may be built up in strong reactive tendencies, helpful at first, but sometimes too rigid and constricting to accommodate the changing conditions of continuous growth. They

influence the range, the pliability and even the nature of personality attributes of later life. It is not intended to imply that all character or personality formation is laid down in these first years after birth, but certainly that essential nuclei do develop then which are the foundations of the later development.

The phase or cycle of life following this (that from five to puberty) is fundamentally different. Superficially we may not be at once impressed with this. For the first part of this era, from five to about ten years of age, shows no dramatic or radical physical changes or functional developments such as have characterized the prenatal and the infantile cycles. The infant is now a child, developing at a fairly steady and consistent rate of growth. He has, under ordinary circumstances, become well established in fundamentals of his own body configuration and functioning. He knows his own sex, his age, his name, his family and various and sundry things about himself and them. His identity is pretty well established in his own eyes, as well as in the records. He may have experienced quite a bit of suffering, separation from parents or even impact with birth and death, depending upon the unique events of his individual fate, but these wisdoms are not inherently laid down in his own genetic unfolding. He remembers now—in a way that he can communicate—events of quite a span of the past, and anticipates with fantasy possibilities of the future. Interestingly, not only is there this relative stabilization of the body, but there is less discrepancy between the two sexes in size and weight and to some extent in interests than at any other time of the active life.

With the fundamental groundwork of physical development and basic emotional experiences laid down, this period from approximately five to ten is one then of marked intellectual expansion. It is the golden time of exploration in which the child learns to read and write and applies these tools to open up enormous vistas of further knowledge. Inevitably he leaves the narrower limits of his family circle and enters into a small sized social life with contemporary rivalries and competition. There is during this time a lessened degree of sexual-emotional tension, probably corresponding to the relative quiescence of the generative organs themselves. Although in some children in whom the infantile period has been unduly chaotic, the sexual interests may actively continue, these seem to have less the effect of crystallized emotional patterning and to take on more of the general exploratory quality which is so

characteristic of the entire gamut of activity of this time. This period between the heightened sexual interest of the five year old and the sharpened recurrence of the sexual drives at puberty has been referred to as the latency period, because it is a time of relative abeyance of these special body drives, and the energy is free for investment in learning and for the reinforcement of early values, habits and ideals. We might rather approximately say that just as the early personality traits have the outline of their origin in the first five years, based on the appetites, controls, and vicissitudes of the unfolding of the body functioning, and the emotional reactions within the family, this latency period is one of solidification and extension of controls, aims, and even ambitions, finding their roots in the social milieu. By some investigators this period has been looked upon as not a true biological stage, but one due to cultural influences and determinants. Considering, however, the total curve of growth and the development of organ systems within the body, we would consider that the relatively even character of the body drives during the first three quarters of the period may mean that this very biological and somatic equanimity is what makes the enormous intellectual and cultural interest possible.

During the *last quarter* of the cycle between five and twelve to thirteen (puberty) the relative stability seen in the regular increase in height and weight each year is again disrupted, by the premonitory changes in the body which will reach a crescendo in the climactic changes of puberty, and mark so very sharply the further differentiation between the sexes. As early as nine to ten, children of both sexes become aware of the incipient changes in their own bodies,—obvious in the beginning development of secondary sex characteristics which alert the child to the imminence of the further changes to come. This is coincident in time with the increased hormonal activity which precedes the grosser pubertal body changes. Whether due to this or just to the influence of the awareness of the already achieved development of siblings or friends who are a little older, many children at this time seem to go through a time of renewed trial of sexual activities and/or a strengthening of the bulwarks against the temptations and distresses attending these. What is striking and noteworthy, however, is that such incidents or experiences, although seeming to occur as the result of external circumstances or the flings of fate, are on closer inspection quite frequently found to be repetitions of earlier quite similar experiences, which have occurred

in the four to six year period. The child does not consciously know that he is testing out again an old experience, for the conscious memory is no longer with him. But the memory traces present in tendencies to act or react in certain ways where there is the slightest similar situation to evoke them, bring out the former pattern combined now with the new situation which has been in part reminiscent of the old but may add new elements of its own. It is not possible to say how frequent is this repetition in actual behavior of the specially constellated pattern from the late infantile period,—but it seems certain that in many children where the actual behavior is not brought into play the fantasies of this period begin to pick up those which have been pretty much inactive for several years.

The changes of puberty initiate the cycle of adolescence,—which literally means the growing into adulthood. Now the most decisive body changes occur, with marked differences between the sexes. Puberty is ushered in by general body growth, and specifically by special growth of the generative organs. The spectacular appearance of the menstrual flow in girls and of the increased capacity for ejaculation in boys announces the approach of that degree of biological maturity which makes parenthood possible. But the discrepancy here between biological potentials and other elements of the personality maturity now becomes strikingly evident. Simply put, boys and girls in their early 'teens *can* produce children, and in some localities do so. But under most conditions of complex living, they are not really ready to do so. The greater diversification and flexibilities of living demand a longer period of education and semi-dependency, and the period of preparation for independent living is relatively longer in man than in any other species. This discrepancy between biological drives and possibility of their fulfillment with resulting inevitable frustration is much more obvious in adolescence, though not so great as the similar discrepancy in the five year old, where frustration is so preordained, and so painful that it is mostly forgotten.

The discrepancy between the biological drives and the socio-economic demands of life is further complicated by the uneven development between the sexes,—since girls mature physically, socially and intellectually as much as a year or two before boys,—and it is only at about fifteen that the weight and age superiority of the boy reasserts itself. These various unevennesses of development tend to create situations of inner tension and strain as well as conflicts with the outer environment. The sudden spurts of growth in themselves sometimes occur so abruptly that the

young person cannot assimilate his own change of size and body contour quickly enough and feels strange, ill-at-ease and awkward, with the inevitable accompaniment of heightened sensitivity. Under these circumstances then, inconsistent behavior and even the appearance of seemingly contradictory character traits occur, especially with rebellion against elders and conservatism toward contemporaries. If there have been too strong emotional ties to the parents at the end of the infantile period, these are re-aroused by the new sexual and aggressive awareness with and following puberty. The special fears and the hostilities resulting from them as well as the direct revival of infantile emotionality itself amalgamates with or runs in opposition to the efforts of the adolescents to find new relationships with contemporaries and new outlets for expanding energetic ambitions for the future. It is the brink of the time when many young people begin an occupation or a career and have practical evidence of incipient economic independence. There is increased drive and activity in all departments of life, but these are not generally smooth running and harmonious. Consequently this cycle appears characteristically as a chaotic one, settling down toward its end when it merges over into maturity, marked more by a legal sign post than by any sharp physiological one—such as indicated its beginning. From the range of vision of the "settled" adult it is hard to realize how unavoidable much of such seeming adolescent disorder is, and how it is part of the inevitably uneven development of this biological era. It seems anything can happen and sometimes almost anything does. Perhaps quiet passive compliance indicates a more serious disturbance at this time, however, than obvious disharmony—since it implies a failure of response to, or too great a fear of the expanding drives which must be a regular accompaniment of coming of age.

We have spent this amount of time sketching the course of the first slope of the bridge of life because it is with the recurrence of the patterns of these cycles leading to maturity that the psychoanalyst must largely concern himself. In the stretch of maturity, roughly between twenty and fifty, the complex mesh of life's drives may appear in three sets of related dynamic patterns sometimes running parallel, always touching and most frequently interweaving in various new intricacies and firmnesses. For the adult now generally marries, becomes one of a pair and presently of a new family group. Not only does marriage itself mean a new kind of identity, or modification of an old one, through the multiple

interactions between the pair; but with the establishment of a family, resonances are multiplied at least to include three generations. In becoming a parent the individual begins to assume some of the identity of his own parent (or in the negative to react against it); he is still himself carrying with him a varying load of incompletely resolved tensions and potential anxieties from his own infancy and childhood; and through his own children he begins to relive both conscious and unconscious repetitions of these, as they combine with the new identity of this next generation. It is not infrequent for life patterns of attitude, interest, ambition—and sometimes even specific fears or other symptoms to be transmitted from generation to generation in this way by the marvellous medium of emotional identification. To the uncritical observer, the result might appear as a true biological heredity, a state of affairs which has its own economical gains as well as liabilities.

It is in this cycle of maturity that psychoanalysis as a technical therapy is most available and generally most useful, and is increasingly sought for those disturbances designated as neuroses or personality disorders which arise from the unduly severe intensification and combination of repetitive emotional patterns, thus seriously impairing the individual's effectiveness.

Understanding based on psychoanalytic principles may be of direct and invaluable service, whether in the formal education of schools or the informal educational influences of less organized groups and social contacts at any time in life. But as a concentrated therapeutic method, it is most effective during the period of greatest individual autonomy and under conditions where elasticity of responsiveness has not been lost and patterns of behavior and attitude have merely crystallized rather than ossified—where there is still expectation of years ahead. Then release or realignment of inner unconscious pressures, achieved only at the expense of time and suffering during the course of analytic therapy, may reasonably lead to greater fulfillment and less distortion of life's satisfactions than has previously been true.

In the *involutional cycle*, by which I mean that period succeeding the long stretch of fullest adult life, there is a gradual recession of both sexual and aggressive drives. Just as at puberty the onset of menstruation in the girl and of ejaculatory ability in the boy are visible, tangible evidences of body change and tend to focus attention on the growing body and emotional capacities,—so in involution the cessation of menstruation

accompanied by the loss of the propulsion of the menstrual rhythm, and the less decisively experienced but equally important reduction of libidinal pressure and potency in the male mark a sense of loss and restriction, causing a review in reverse of the expectations and ambitions of adolescence and young maturity. Consequently these reductions, felt as clear and real threats to the fullness of life again arouse the old reactions to similar threats from the earlier eras, and combining with the actual limitations of the future give rise to states in which disappointment and regret may play overwhelmingly large parts. Great individual variability exists, however, in the speed and extent of involutional changes. Consequently particularly in the earlier part of this era, psychoanalytic treatment may be useful, depending upon the special indication and conditions attending it.

In the final cycle of life—old age or senescence, the *aged* are entitled to conserve that rest and special equilibrium which the ebbing of life's drives may permit, a period then in which memory becomes more an indulgence and less of a pressure.

We shall make no effort in this presentation to deal with psychoanalysis as a technique of therapy, beyond emphasizing that its goal is to increase the genuine self-possession, by loosening the constricting tensions of the past, and thereby delivering the present more nearly into its own. It is a method through which current attitudes are modified through making the individual conscious of the special precipitates of experience no longer remembered by him—converting one kind of memory capable of unknown pressures of its own into a form more clearly recognizable by the person and less likely to produce direct action. In doing this, both individual choice and its corollary, responsibility, are increased. Thus, in the very process of delivery and re-experiencing of these out-dated disturbances, a release of energy and a new alignment of forces within the individual occur. Its fundamental principles are relatively simple, but their therapeutic application is unusually exacting and painstaking.

I would especially stress again, that valuable as psychoanalytic therapy is in the handling of neurotic disorders, it would still seem that its greater and wider contribution lies in its research value and the new dimension of understanding which it has given in problems of human behavior,—whether in the fields of psychiatry, psychology and medicine, or in related fields of sociology, education, and even literature and history.

NEW YORK PATHOLOGICAL SOCIETY

*Abstracts of Papers**

Presented at the Meeting, December 18, 1952 at The New York Academy of Medicine

Some Clinicopathologic Aspects of Muscular Dystrophy

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Three problems were discussed. The first dealt with the occurrence of lesions in the myocardium in systemic cases of progressive muscular dystrophy. Alterations of the myocardium comparable to those encountered in skeletal muscles affected by dystrophy were found in eight of fourteen cases. Clinically most patients did not exhibit evidence of cardiac disorder, but arrythmias and tachycardias may occur and a few may go into congestive heart failure. The size of the heart may be as large as 600 gm. despite the absence of hypertension.

The second part dealt with the specific involvement of the extraocular muscles by dystrophy. A family was encountered in which ptosis and external ophthalmoplegia first were noted at about twenty years of age. There was no diplopia and the disease progressed slowly over many years. The first patient affected by this disorder died and was autopsied; this made possible examination for the first time of both the central nervous system and the extraocular muscles. There were no abnormalities of the motor nuclei of the ocular complex, but the muscles themselves were characteristically dystrophic. This male patient had two sons who have been affected by the same disorder without evidence of involvement of muscles elsewhere in the body. A third generation may possibly be affected in this family. The question of "chronic progressive nuclear ophthalmoplegia" was reviewed and the conclusion drawn that these cases are instances of ocular myopathy. The isolated occurrence of ocular myopathy demonstrates that striated muscles may be involved selectively; cardiac myopathy demonstrates that any striated muscle may be affected.

The final discussion had to do with the occurrence of dystrophy late in life—past the age of thirty years. Appropriate cases were considered. Reliably reported cases of dystrophy have occurred as late as the seventy-seventh year of life. The schemes of classification of dystrophy were reviewed with particular emphasis on the over-simplification inherent in them. It was shown that dystrophy may affect any group of striated muscles proximally or distally, focally or in widespread fashion, may occur in either sex, may be sporadic or familial, and may begin in any year of life from infancy to old age. It was emphasized therefore that the dystrophies form a wide clinical spectrum. Many cases may fall into convenient slots but variations may be great.

DISCUSSION

ADE T. MILHORAT: I should like to congratulate Dr. Netsky on his informative talk. I believe Eulenburg and Cohnheim[1] in 1865 were the first to study the heart in muscular dystrophy, but demonstration of actual involvement of the cardiac muscle had to await the observation of Ross[2] who

* Manuscript received March 1953.
† By invitation.

found atrophy of the fibers, and increase in the interstitial connective tissue in the heart of a boy aged twelve years. Many observations have since been made indicating that the occurrence, in the heart, of lesions resembling those seen in the skeletal muscles is not rare in muscular dystrophy. Evidence, other than histopathologic, of cardiac involvement, includes tachycardia, an absence of the decrease in pulse rate that occurs in normal subjects during sleep, and changes in the electrocardiogram.[3, 4] How ver, actual complaints referable to the heart are unusual, and cardiac failure is seen infrequently. The limited activity of patients in the advanced stages of muscular dystrophy when cardiac changes are most likely to occur, probably is a factor contributing to this infrequency of obvious cardiac symptoms.

In our preoccupation with the extensive degenerative changes that occur in the skeletal muscles, many of us are apt not to consider the lesions in the myocardium. Dr. Netsky's convincing demonstration is important in emphasizing the extent to which the heart muscle may be involved, and the frequency with which these changes may occur. We do not know the biochemical basis of the degenerative changes or why one type of muscle is more extensively involved than the other. We do know that there are certain biochemical differences in these two types of muscle, but whether these chemical differences are related to the differences in the extent of structural involvement in cardiac and skeletal muscle can be only a matter for speculation for the present. For example, the concentration of creatine in normal human striated muscle is about 400 mg. per 100 grams; it is lower in cardiac muscle, and considerably less in smooth muscle. Degenerative changes are most pronounced in the striated muscle, less in the cardiac muscle and it is questionable whether they occur in smooth muscle.

I should like to emphasize what Dr. Netsky has said regarding the usual clinical course of muscular dystrophy. While the first manifestation of the disorder may be weakness and wasting of a few muscle groups, the process almost always extends and eventually involves most of the muscles of the body. An exception to this rule may be seen in certain patients with the facioscapulohumeral type of the disease in whom weakness of a few muscles of the face or shoulder area may for many years or even for the entire life span of the individual be the only evidence of this disorder. Davidenkoff[2] reported on the occurrence of abortive forms of muscular dystrophy with wasting in isolated muscle groups or with congenital absence of one or more muscles. Other members of the family, and often children of these persons, had typical muscular dystrophy that was progressive.

Of particular interest was the description of the family with muscular dystrophy limited to the extraocular muscles. I have not seen any such families among the very large series of patients observed by us.

One disorder in which the manifestations may be multiform, but in which only one or a few changes may be present for many years or even during the entire life of the individual, is myotonia atrophica. The manifestations include muscular wasting, often first seen in the sternocleidomastoid muscles and in the muscles of the face, myotonia, ptosis, bilateral cataracts, bradycardia and testicular atrophy. Most of these abnormalities tend to increase. For example, the muscular wasting may become generalized, but myotonia may decrease as the muscular atrophy advances. It is not unusual to observe in the families of patients who exhibit all of these changes other members in whom limited muscular wasting or myotonia alone may be present. Of special interest is the occurrence of cataracts as the only manifestation of the disease. The cataract is of characteristic type and is best demonstrated by slit lamp microscopy. It is of interest that in the family described by Dr. Netsky myotonia or other symptoms of myotonia atrophica were not demonstrated. Were cataracts seen by slit lamp microscopy? Inheritance might have been by a dominant factor. This type of hereditary transmission is seen in the facioscapulohumeral form of muscular dystrophy, whereas in the pseudohypertrophic form of childhood, inheritance by a sex-linked recessive factor is generally the rule.

Dr. Netsky's remarks on classification are

important. I agree that there often is overclassification, and a number of years ago, as a reaction to this, I grouped all types of the disease together into one large unit under the name "muscular dystrophy." However, a useful purpose actually is served by our recognition of these difficult types. These different forms of the disorder have certain characteristic clinical features, e.g., pseudohypertrophy as an outstanding feature of the pseudohypertrophic form, and weakness of the facial muscles as an early change in the facioscapulohumeral form, often preceding by many years onset of wasting in other muscles. Moreover, inheritance and the clinical course differ in these different forms. Thus, the classification into these commonly recognized types may be of aid in diagnosis and prognosis, but in our present state of knowledge this classification should not imply any fundamental difference in pathogenesis.

While muscular dystrophy usually begins early in life, it is not rare to observe patients in whom symptoms first were noted after the ages of forty or fifty and in whom the findings on all examinations and tests are identical with those of other forms of muscular dystrophy. We have designated these cases as "muscular dystrophy of late onset." None of our patients gave evidence of inheritance of the disease. The clinical course often is slow, but, on the other hand, it may be very rapid with complete infirmity in a year and termination in death within two years. It is important in considering this group of patients, to keep in mind that myositis may simulate muscular dystrophy. Pain, tenderness and fever may be absent, and muscular wasting may be masked by diffuse edema. Although the edema may not be demonstrable on clinical examination, the considerable reduction in the urinary output of creatinine often observed in these patients will indicate advanced muscular atrophy. In other words, rapidly advancing muscular wasting without diminution in gross volume should suggest the presence of edema. Edema is not a feature of muscular dystrophy, but is of common occurrence in myositis. Cardiac lesions resembling those in the striated muscles are not uncommon.

In brief, one may say that in most instances classification is relatively easy, but many patients cannot be grouped as having any of the generally recognized types of the disease. The process is one that may affect any or all of the skeletal muscles; the cardiac musculature likewise may be involved, and the nature of the underlying pathologic process is not known.

BRUNO VOLK: Dr. Milhorat mentioned that changes in the smooth muscle tissue may occur. I have noticed in a much smaller material than that of Dr. Netsky that replacement of the smooth muscle of the intestine may take place and it is occasionally mentioned in the literature. These areas are very small, and not as conspicuous as those seen in the heart. I wonder if Dr. Netsky has had the opportunity to examine carefully sections of the intestine and found a replacement fibrosis.

JOHN M. PEARCE: Both Dr. Netsky and Dr. Milhorat mentioned the fact that these patients do not seem to suffer from cardiac difficulty. Some of them do die in cardiac failure suddenly, do they not?

ADE T. MILHORAT: That is true.

MARTIN G. NETSKY: As far as the problem of myotonia is concerned, we are well aware that such a condition has to be distinguished from what we described as ocular myopathy. None of these patients had any stigmata of myotonia. Furthermore, while myotonia atrophica can occur sporadically and affect one or another part of the body, it would be very unusual for it to occur in two successive generations, and perhaps in a third generation, always in the same form. I have gone over numerous pedigrees of myotonia atrophica and have not encountered such a uniform inheritance; so I do not think the condition I have discussed is myotonia atrophica. In the dystrophies occurring late in life myotonia must be considered, but if it cannot be found in the patients, or any of the other generations, I think one can rule it out.

In reply to the question about dystrophy affecting the smooth muscle of the intestine,

I have never seen that. We had one case where we thought the smooth muscle of the urinary bladder was scarred, but I have never seen it in the intestine.

SILIK H. POLAYES: Is there anything in the biochemistry that might aid in the classification?

MARTIN G. NETSKY: I would say no.

ADE T. MILHORAT: My answer likewise would be no. Creatinuria is not specific. Usually it is more pronounced in the childhood form of muscular dystrophy, but the magnitude of creatine elimination is determined in part by the presence of normal physiologic creatinuria. By the time the patient reaches an age when the physiologic creatinuria normally has subsided, the disease is advanced. In the facioscapulohumeral type of the disease, creatinuria may be minimal for periods of many years, but eventually when the disease has involved most of the muscles, creatinuria is definite. All one can say is that when creatinuria is pronounced one may assume that the muscular involvement is extensive, but this does not define the type of the disease.

JOHN M. PEARCE: Are there any parallel changes in the various liver function tests?

ADE T. MILHORAT: No, there are not. I wish that more comprehensive and definitive data on liver function were available. When we speak of muscular dystrophy as a primary muscular disorder, our thinking often is in terms of a few generations ago when the outstanding question was whether the muscular wasting is, or is not, subsequent to some demonstrable change in the nervous system. We have perhaps become fixed in our idea that we are dealing with a morbid process that has its onset in the muscle, when, as a matter of fact, the muscle may be the end organ in which obvious pathologic changes occur, but the primary metabolic alteration may be elsewhere. Therefore, the question regarding liver function tests is pertinent and provocative.

MARY A. MARCUS: Are there characteristic changes in the blood?

ADE T. MILHORAT: In one type of muscular dystrophy, namely the experimental form induced by deprivation of vitamin E, an abnormal electrophoretic pattern of the plasma proteins occurs, but similar changes are not seen either in the clinical forms of muscular dystrophy or in the muscular degeneration produced by administration of large amounts of cortisone.

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*Studies on the Nature and Pathogenesis of Muscular Degeneration in Cortisone-Treated Rabbits**

JOHN T. ELLIS

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Muscular lesions have been noted by others in cortisone-treated animals, but they have not been described in detail and their pathogenesis has not been considered. In experiments undertaken for other purposes,

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we have recently observed widespread degeneration of skeletal muscles following the administration of massive doses of cortisone to rabbits. Observations on the nature and pathogenesis of the changes in the muscles are here reported in brief.

Voluntary muscles were procured from the trunks and extremities of thirty-seven young rabbits given cortisone intramuscularly, 10 mg. per kg. per day, for periods of seven to twenty-one days or longer; all regularly displayed degenerative changes that became more severe with the passage of time. When examined after seven to fourteen days, large segments of many of the fibers in each muscle were swollen to 3 or 4 times their normal size; these were much paler in fixed and stained preparations than were the adjacent unchanged segments within the same sarcolemmal sheaths and their structure was homogeneous and devoid of identifiable myofibrillae; occasionally lipids and calcium salts, separately or together in small amounts, were deposited in them. The protoplasm of the swollen segments was actually necrotic, for it was more or less promptly phagocytosed by mononuclear cells, which soon became conspicuous within stretched and sometimes ruptured sarcolemmal sheaths and not infrequently formed syncytial giant cells as they encircled the necrotic material. After twenty-one days, some 40 to 80 per cent of the muscle fibers visible in any given field displayed the segmental swelling and necrosis just described. In addition, atrophy of the uninvolved fibers was widespread. Fibrosis was not present, though interstitial edema with occasional mononuclear inflammatory cells was regularly seen. Complete healing of the muscular degeneration occurred after the cortisone injections were discontinued as was shown by the following observations. Each of five rabbits given cortisone for twenty-one days manifested segmental degeneration of voluntary muscle fibers, as determined by biopsy of the sacrospinalis muscle at the end of this period. When these animals were sacrificed six, twelve, sixteen, twenty-one, and twenty-two weeks after the cortisone had been discontinued, their muscles were histologically normal in every instance.

The necrotic changes, when viewed in the large, are seen to resemble closely those described in Zenker's degeneration of skeletal muscle, in potassium deficiency, in vitamin E and other deficiency states, and in muscles of mice infected with the Coxsackie virus. No such abnormalities were observed in the cardiac and involuntary muscles of the cortisone-treated rabbits, and skeletal muscles of sixty-five control and five starved rabbits likewise failed to disclose them.

In order to compare the cortisone-induced degeneration with potassium deficiency nine rabbits were placed on a diet deficient in potassium. All rabbits on the deficient diet developed voluntary muscular lesions indistinguishable from the cortisone-induced muscular degeneration, but differed significantly in that every animal developed severe myocardial necrosis as well.

To learn more about the cortisone-induced lesion, chemical analyses were made on necrotic muscles procured from six rabbits treated with the drug for periods of ten to twenty-two days, and on normal muscles from eight controls. Half of each muscle was used for histologic study, the rest being analyzed for water, lipids, nitrogen, sodium, and potassium. When compared with the controls, the necrotic muscles exhibited slight increases in content of water (average 78.2 per cent; controls 77.3 per cent) and larger increases in lipids (average 2.2 per cent; controls 0.7 per cent); they contained similar amounts of nitrogen (average 14.66 per cent on fat-free samples), and they had lost significant amounts of potassium (average 42.6 mEq/100 gm. dry fat-free muscle; controls 53.5) while gaining corresponding amounts of sodium (average 27.1 mEq/100 gm. dry fat-free muscle; controls 9.1). Cardiac muscle from the cortisone-treated rabbits did not display these chemical alterations.

DISCUSSION

ADE T. MILHORAT: I believe everyone will agree that this was a beautiful presentation of an important investigation. Dr. Ellis stated the opinion that the structural changes produced by cortisone probably represent a general type of reaction of the skeletal muscle to a number of injurious

influences. For example, one sees similar changes in rabbits during vitamin E-deficiency, and in suckling mice subsequent to injection with Coxsackie virus. However, one would not be justified in concluding that the significance of these studies is merely the demonstration of another form of experimentally produced muscular dystrophy. I think that it is a great deal more than that. Cortisone is a useful therapeutic agent in a number of diseases. When employed during the early stages of dermatomyositis, the therapeutic effects of cortisone or ACTH may be dramatic; although the effects may be much less or even absent during the late and chronic stages of the disease. It is of interest that the histologic changes in skeletal muscle in dermatomyositis may be indistinguishable from those described by Dr. Ellis. In progressive muscular dystrophy, the administration of cortisone or ACTH usually increases creatinuria. One may speculate, perhaps with profit, on the possible significance of Dr. Ellis' findings with reference to the problem of the pathogenesis of muscular dystrophy in man. Certainly, in investigation of this serious crippling disease, the etiology of which is unknown, this lead cannot be disregarded.

When Dr. Ellis first informed us of his observations, we naturally were interested in knowing whether the biochemical alterations in this type of muscular dystrophy differed from those that occur in the muscular dystrophy resulting from vitamin E-deficiency. Dr. Anne Milman in our laboratory observed that in both forms creatinuria was pronounced, and could be terminated quite promptly, in the first form by discontinuing the injections of cortisone, and in the second form, by administering vitamin E. It is of interest that there was no pronounced retention of sodium in the rabbits given large doses of cortisone, whereas appreciable sodium retention occurred in the vitamin E-deficient animals. Calcium retention, as measured by urinary output, is an early change in vitamin E-deprivation, but was absent in the cortisone treated animals. It is apparent that we do not know enough about these alterations in metabolism of calcium, since despite the differences in urinary output, calcification of the muscles may be present in both forms of muscular dystrophy. Increased elimination of urinary potassium was observed in the two types of muscular degeneration. It is my opinion that in all types of muscular wasting in which such determinations have been made, decrease in the concentration of potassium and glycogen in the muscle was observed. We did not make these determinations in our animals. The metabolic changes I have mentioned may occur before the onset of creatinuria and of clinical signs. It is not known whether they are secondary changes, or are related closely to the primary process.

Dr. Ellis administered potassium to his animals to rule out the possibility that the muscular degeneration might have been the result of loss of this substance. The fact that potassium supplementation did not prevent or decrease the muscular damage is of interest. However, I do not believe these observations necessarily are definitive; determination of actual loss or retention of potassium would be informative. Our studies on the effect of ACTH on potassium metabolism in a patient with myotonia atrophica are pertinent. During a period of seven days when the patient was given 100 mg. ACTH daily, he lost 180 mg. potassium per day on an intake of 2.85 gm. During a subsequent period of five days, the daily administration of 200 mg. ACTH induced a negative balance of 1.64 gm., despite an increased dietary intake of 4.55 gm. daily. In other words, despite the additional intake of potassium, the actual loss of this substance from the body was increased.

The changes in fat metabolism must be pronounced, since the blood serum of these animals was rather milky in appearance. The altered electrophoretic pattern of the serum proteins which we observed in vitamin E-deficiency does not occur in animals with muscular dystrophy produced by cortisone nor in patients with progressive muscular dystrophy.

JOHN M. PEARCE: We are all wondering what happens to the muscles of the patient who has hyperadrenalism or an adrenal tumor. I am constantly getting biopsy specimens from patients, and I have

never seen much in them. Another thing which strikes me as interesting is the complete regeneration of these muscles after cortisone administration is stopped. I think most of us teach our medical students that muscle does not regenerate. Will Dr. Ellis tell us about that? I think he is probably right about the chemical changes being secondary to the muscular atrophy rather than primary. I would like to know how the muscle and the skin tie up in such conditions as dermatomyositis. I am sure I am not the only one who has questions.

STANLEY M. ARONSON: Dr. Ellis has pointed out that the lesions are morphologically indistinguishable from those of the myositis caused by the Coxsackie virus, the poliomyelitis virus and numerous other viral pathogens. When we consider this in conjunction with the fact that one of the actions of cortisone is the enhancement of a multitude of infectious diseases, and that when cortisone alone is given to genetically different experimental species, from mice to monkeys, latent infections have been shown to emerge, in the light of this aspect of cortisone activity, I should like to inquire whether any work has been done to exclude the presence of some viral pathogen in these foci of myositis.

THOMAS G. MORRIONE: When one attempts chemical analyses of tissues he is apt to encounter many pitfalls. We encountered one such situation with butter yellow carcinogenesis in rats, namely, the alkaline phosphatase determination of livers. We were led to assume by chemical analysis that there was considerable elevation of alkaline phosphatase in hepatoma produced by the administration of paradimethylaminoazobenzene, but as we went into the problem further, we found the elevations were primarily in the proliferating bile ducts rather than in the hepatoma. Similarly, I wonder whether in Dr. Ellis' studies one should conclude that the chemical alterations which he observed occurred in the skeletal muscle fibers themselves. Is the elevation of sodium an elevation of sodium in the interstitial fluid? Is the lipid increase merely an increase in lipids due to fortuitous inclusion of hyperlipemic serum within the muscle?

SIGMUND L. WILENS: It was not clear to me whether all the muscle groups were equally involved, or whether certain muscle groups were spared.

SILIK H. POLAYES: What becomes of all the reactive structure within and around the muscle? Does it completely disappear? It is almost inconceivable that so much reactive tissue, including the giant cells, fibroblastic proliferation, etc., which was demonstrated, would leave no trace whatever.

ALFRED ANGRIST: What did the adrenal show in these animals?

JOHN T. ELLIS: I agree that there are many pitfalls in interpretation of chemical analysis of tissues. We do not feel that chemical analyses of the muscles which we have presented significantly aid in understanding the pathogenesis of the cortisone-induced muscular degeneration. It is quite likely that the described chemical alterations represent changes secondary to muscle degeneration and are in no way specific for the cortisone-induced lesions.

We have not performed experiments which provide definitive evidence to exclude a possible viral etiology of the cortisone-induced muscular degeneration. The absence of other visceral lesions usually associated with known viral infections, and prompt recovery as soon as cortisone is discontinued provide indirect evidence against an infectious etiology of this lesion. The pathogenesis of the muscular degeneration is unknown, however.

In general, all muscle groups are involved by the degenerative process.

The sequence of the healing stages has not been investigated, however, our observations indicate complete restitution of voluntary muscle occurs six to twenty-two weeks after cortisone is discontinued. Regeneration of voluntary muscle, in contrast to cardiac muscle, has been previously reported in humans as well as in experimental animals.

NEW YORK PATHOLOGICAL SOCIETY—Continued

*Abstracts of Papers**

Presented at the Meeting, January 29, 1953 at The New York Academy of Medicine

Reminiscences on Ferritin

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A study of the magnetic susceptibility of ferritin began in the laboratory of Dr. L. Michaelis about 1941. The work led to an understanding of the properties of this compound, how to recrystallize and purify it, and how to remove the iron without denaturing the protein apoferritin. The iron appears to be in the form of micelles situated on the surface of the protein. The iron hydroxide micelles are further characterized by a magnetic susceptibility of 3 unpaired electrons per iron atom, a value which is different from all other iron compounds of the body. Evidence, from extraction of ferritin and tracer studies, was obtained supporting the view that ferritin is the normal iron storage protein of the body.

It was later found, using a micromethod, that the feeding of iron to a guinea pig induces the formation of ferritin. Within seven hours after an iron feeding the ferritin content of the duodenal mucosa is at a maximum. Thus the absorption of iron by the mucosal cells results in an increase in the amount of a specific protein apoferritin to which the iron attaches in the form of iron hydroxide micelles. Whether the increase of ferritin in the mucosa in response to iron feeding is directly or only indirectly connected with the mechanism of the mucosal block cannot be decided from these experiments.

Some Aspects of the Metabolism of Iron

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The excretion of iron from the body is very limited, the iron content being regulated principally by controlled absorption. In normal dogs this control is such that only 1.5 to 6 per cent of an oral dose of iron salts will be absorbed. In general, the larger the amount of iron administered, the smaller the percentage absorbed. Some iron is absorbed by the colon, but most is taken up by the stomach and small bowel. No adequate data are available, however, on the absorption from various levels of the gastrointestinal tract.

In the iron-deficient dog absorption of

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TABLE I—TRANSFUSION SIDEROSIS
Distribution of Pigment

Transfusions	*No. Cases*	*Pigment Disposition*							
		Liver	*Spleen*	*Pancreas*	*Skin*	*Gut*	*Heart*	*Kidneys*	*L. Nodes*
<20	3	3	2	1	0	0	0	1	1
20-60	8	8	6	1	0	1	1	1	4
60-100	5	5	2	4	0	1	2	4	4
>100	9	9	7	5	4	5	5	7	5

TABLE II—TRANSFUSION SIDEROSIS
Occurrence of Hepatic and Pancreatic Fibrosis

Transfusions	*No. Cases*	*Increased Fibrous Tissue*						
		Liver				*Pancreas*		
		None	*Slight*	*Mild*	*Severe*	*None*	*Slight*	*Mild*
<20	3	0	0	0	3	2	1	0
20-60	8	3	1	2	2	5	2	1
60-100	5	1	0	2	2	3	1	1
>100	9	6	1	1	1	6	2	1

iron is increased over that of normal animals. As much as 16 to 66 per cent of a single oral dose of radioactive iron may be taken up. The isolated stomach can absorb considerable quantities. Likewise, it is readily absorbed through a jejunal fistula, but not as efficiently as from the entire tract. Very little more than normal is absorbed from the colon of the iron-deficient dog.

Attempts to increase the absorption in normal dogs by anoxia of forty-eight to fifty hours' duration have been unsuccessful. Nor is it increased in the brief period of anemia produced by a single large bleeding.

It has been suggested that the level of iron in the plasma may be a factor in controlling absorption from the alimentary tract. To test this point, iron was injected intravenously into dogs over a period of several hours. During this period a test dose of radioactive iron was administered orally. It was found that absorption was not inhibited by the high plasma levels of iron, either in the normal dog or in the iron-deficient animal. This would seem to indicate that the plasma iron level does not directly control absorption.

A second possibility is that iron absorption is controlled by the iron content of the mucosal cells of the alimentary tract. The following experiments are significant in this connection. Large amounts of iron were fed to iron-deficient dogs. Several hours later, after the iron had passed into the lower intestinal tract, a small test dose of radioactive iron was given orally. Under these conditions its absorption was found to be depressed. Presumably the first dose—a large one—increased the iron content of the intestinal cells to the point of producing a "mucosal block" to further absorption. This apparent block persisted for less than twenty-four hours in these iron-deficient dogs.

It would appear, however, that factors other than the "mucosal block" may also be important in regulating iron absorption. Thus, in pernicious anemia, in "aplastic" anemia, and in human cases of hemolytic anemia, iron absorption is increased. The same is true for carefully controlled experi-

TABLE III—TRANSFUSION SIDEROSIS

Distribution of Pigment Related to Number of Transfusions and Interval from First Transfusion to Death

Transfusions and Duration	*No. Cases*	*Pigment Disposition*							
		Liver	*Spleen*	*Pancreas*	*Skin*	*Gut*	*Heart*	*Kidney*	*L. Nodes*
No. > 100 / Yrs. > 4	3	3	2	3	3	2	2	3	3
No. > 60 / Yrs. > 4	4	4	2	4	3	2	2	3	3
No. > 100 / Yrs. > 3	8	8	5	6	4	4	4	6	7

ments in which hemolytic anemia is produced experimentally in dogs through the prolonged administration of acetylphenylhydrazine. Under these various conditions there is presumably no reduction in the iron content of the mucosal cells. At any rate, there is no overall deficiency of bodily iron.

It would appear, furthermore, that alterations in iron absorption may occur altogether independently of anemia. Thus, deficiency of bodily copper suppresses iron absorption in rats. On the other hand, the absorption of iron can be greatly increased by the administration of diets in which corn is the principal source of protein. While the phosphorus content of the diet influences iron absorption under these circumstances, other dietary factors also seem to be involved.

From the data available, therefore, it seems that under ordinary circumstances the intestinal mucosal cells are capable of regulating the absorption of iron, that this function is somehow related to the amount of iron present in the cells, and probably to the amount of ferritin present. In the face of prolonged anemia or severe dietary restrictions, however, this mechanism fails and excessive amounts of iron gain entrance to the body. The reasons for these latter phenomena are under investigation, but as yet no wholly satisfactory explanation is apparent.

In addition to the problem of iron absorption, there are other problems of iron metabolism that are of interest. Of particular pertinence is the relationship of transfusion siderosis to hemochromatosis. This is currently a somewhat controversial subject, and various opinions have been expressed. We have tabulated certain anatomic findings in twenty-five cases of transfusion siderosis. Four of these cases are from the Presbyterian and Delafield Hospitals; the others have been taken from the literature. Only those cases are included in which the autopsy reports were relatively complete. Tables I to IV show the number of transfusions, duration of transfusion, distribution of hemosiderin in certain organs, and the presence of pancreatic or hepatic fibrosis.

It seems evident from a study of these tables that the distribution of hemosiderin in transfusion siderosis can mimic that seen in hemochromatosis. There may even be pigment in the ductal epithelium of the liver and pancreas, but only if many transfusions have been given over a long period of time. This observation may mean that the distribution of iron-containing pigment (and perhaps other particulate matter) is not specific for any particular disease, but rather is related to the quantity present and the time during which it has been present. The tables also suggest that the cirrhosis of the liver and pancreatic fibrosis cannot be attributed to iron excess alone. This latter finding is in accord with the experimental results of several investigators.

DISCUSSION

RALPH ENGLE: Dr. Granick's very interesting story of his work with the ferritin-apoferritin system has interested me very

TABLE IV—TRANSFUSION SIDEROSIS

Occurrence of Hepatic and Pancreatic Fibrosis in Relation to the Number of Transfusions and Duration

Transfusions and Duration	*No. Cases*	*Increased Fibrous Tissue*						
		Liver				*Pancreas*		
		None	*Slight*	*Mild*	*Severe*	*None*	*Slight*	*Mild*
No. > 100 / Yrs. > 4	3	2	1	0	0	2	1	0
No. > 60 / Yrs. > 4	4	2	1	0	1	3	1	0
No. > 100 / Yrs. > 3	8	5	1	1	1	6	1	1

much. His work has become more or less a keystone in our thinking about the problem of iron metabolism. I am sure you all join with me in visualizing the absorption of iron through the mucosa of the intestinal tract, starting with the incorporation of iron into apoferritin forming ferritin and its later release and absorption into the blood stream. I would like to ask Dr. Granick whether any extensive work has been done in trying to visualize the ferritin crystals in the mucosa in human beings. It would seem that this would not be too difficult a task to do at operation or even at autopsy in a variety of conditions, with possibly some attempt to quantitate this information. Has that been tried? I should think that would interest a group of pathologists who have considerable material available.

The second paper was also very instructive. It was a very complete summary of our knowledge of iron absorption. The question frequently arises clinically as to whether hydrochloric acid in the stomach has much, if any, effect on absorption of iron from the gastrointestinal tract, and also what possible effect reducing substances might have. Does Dr. Stewart have information on this subject gained from his experiments in dogs? Dr. Stewart's reference to the interesting work on mucosal block brought to mind a case recently seen by Drs. John Ellis, Carl Smith and Irving Shulman at The New York Hospital. This was a patient with Cooley's anemia, who had a high iron level in the circulating blood, and in spite of a very few blood transfusions, developed a typical picture of hemochromatosis with much more iron present in the organs of the body than could ever be accounted for on the basis of the iron administered in the transfusions. It was felt that in all probability the mechanism for the absorption of iron was defective and that the patient absorbed considerably greater quantities of the iron than would have been desirable.

S. GRANICK: Concerning the question of whether one could use this micromethod for detecting ferritin or differences in ferritin in the gastrointestinal tract, this has been done in horses, and more or less runs along the same lines as in the guinea pig. In the case of humans, we did one experiment. We were interested in seeing whether in hemosiderosis or hemochromatosis the mucosal block was either not present at all or was damaged. If ferritin had not been found, we might have concluded that a mucosal block was not present; thus more iron would get in. The absence of ferritin would parallel high iron absorption. However, in one case of hemochromatosis, on addition of $CdSO_4$ to scrapings of the duodenal mucosa, ferritin crystals were found. This was not done quantitatively, but merely qualitatively. The very fact that ferritin crystals are present in hemochromatosis could be interpreted as indicating that at least the mechanism for the production of the spe-

cific protein and the combination of the iron with this protein are normal. One could not tell in this experiment if the quantity of this material is diminished.

WELLINGTON B. STEWART: It is stated that hydrochloric acid aids the absorption of iron. I have never seen any convincing data along those lines, and as I mentioned before, patients with pernicious anemia who should not have any acid in the stomach have absorbed large quantities of iron.

To answer the question of reducing substances, that is, whether the iron is in the ferrous or ferric form, iron is presumably absorbed in the ferrous state, and in the human it makes a difference whether the iron, when given by mouth, is ferric or ferrous iron. I believe the guinea pig and some other animals have enough reducing substances in their saliva to reduce ferric to ferrous iron. In the dog it makes no difference whether we give ferrous or ferric salts; the absorption is the same.

The problem of Cooley's anemia and iron metabolism is interesting. An individual with Cooley's anemia would be presumed to absorb increasing amounts of iron because of the anemia. It has long been known that there are profound abnormalities in pigment metabolism associated with that disease. Children dying of Cooley's anemia have large deposits of iron- and non-iron-containing pigments similar to those found in hemochromatosis. Hence I am not surprised that a person fifteen years of age with thalassemia had large amounts of iron in the liver.

IRVING M. LONDON: I am grateful for the opportunity of being here, and I enjoyed both papers. With respect to the problem of ferritin and apoferritin, I should like to ask Dr. Granick whether one can isolate and crystallize apoferritin as such in the absence of iron, or must one isolate ferritin by precipitation with cadmium sulfate and then obtain the apoferritin by splitting off the iron? This is pertinent to the question of whether apoferritin is being synthesized constantly or only in response to the stimulus of iron. Dr. Granick and I were talking at dinner about the somewhat analogous problem of hemoglobin formation. Can one dissociate globin and heme formation? Can one demonstrate the formation of apoferritin in the absence of iron?

Just a brief comment about the problem of interpreting data on the absorption of iron in terms of the incorporation of iron into circulating red blood cells. Dr. Stewart pointed out very properly the danger that is inherent in assuming that iron absorption can be measured in terms of the iron incorporated into the red blood cells in circulation. I should like to emphasize this point. In pernicious anemia, for example, there is evidence for increased utilization of iron for heme synthesis and yet a significant portion of this heme may not leave the bone marrow as hemoglobin of circulating erythrocytes. In such a case there may be considerably greater absorption of iron than would be reflected in the iron utilized for hemoglobin in circulating erythrocytes.

IRVING GRAEF: The subjects covered tonight are of particular interest to some of my colleagues and myself because of our opportunities for studying about a dozen patients who have had large numbers of transfusions; among these five developed evidence of iron deposition in their tissues which on histologic study did not differ from that seen in endogenous hemochromatosis.

Since we reported our findings before this group two years ago we have been pursuing the matter further in different ways, looking for reasons to account for the differences in the controls who had had similar numbers of transfusions, but who did not develop histologic evidence of hemochromatosis, merely having the conventional hemosiderin deposits in the usual situations in the reticuloendothelial system.

The comments regarding hemochromatosis made by Dr. Stewart are particularly pertinent, and they outline the problems which all of us have to solve in our own fashion as we encounter these patients.

I want to call your attention to the patients with cirrhosis of the liver antedating a hemolytic episode, and the question as to how the cirrhotic liver behaves in the pres-

ence of excess iron. The problem of the discrepancy between the amount of iron given in the transfused blood and the amount of iron found in the liver has been mentioned repeatedly, here and in the literature. The converse relationship exists; there are instances of excess deposit in the liver without the histologic reactions characteristic of hemochromatosis.

Then there is the question of a change in the iron metabolism associated with transfusions, a change which may endure and persist for a long time after transfusions.

We have recently been fortunate in encountering several patients who might be labelled as representing "inter-grades" between endogenous hemochromatosis and the so-called exogenous type. Dr. Wilens of Bellevue Hospital has permitted me to study two cases of quite different types associated with hemolytic anemias. At necropsy of both, the iron deposits found in the liver and the pancreas, and limited to these situations, were like those seen in endogenous hemochromatosis. One of these cases I should like to mention in detail. The patient, a Negro thirty-seven years of age, had been studied four times in Bellevue for different illnesses. He had a long history of alcoholism and the diagnosis of alcoholic cirrhosis had been made several times. Six months before his death a liver needle biopsy was done, and this was reported as showing conventional portal cirrhosis. Iron stains were *negative*, using the Turnbull technique. Four months later the man developed an acute infection of the respiratory tract, and during this illness showed his only hemolytic crisis in which the hemoglobin fell from 14 to 4 grams, and at that point when the hemoglobin was falling, sicklemia was observed for the first time in fresh smears. He died in this illness, and at necropsy his liver showed enormous iron deposits. That was six months after a negative liver biopsy obtained by needle. His pancreas contained iron deposits in the acinar epithelium and the pancreatic duct epithelium, with considerable interlobular fibrosis, containing macrophages laden with iron.

I do not know quite where to classify this case, and the occurrence of these inter-grades seems to me an expression of special circumstances which permit iron to deposit in certain cells in certain individuals.

I would also invite your attention to the several recent reports of disturbances in serum iron in acute hepatitis and in chronic hepatic disease. I would like to hear Dr. Stewart and Dr. Granick comment on these special types of cases.

CARL H. SMITH: The problem of iron absorption and tissue changes in connection with chronic hemolytic anemia has interested us for many years. In our out-patient Transfusion Clinics at The New York Hospital, approximately twenty children with severe Cooley's anemia and two children with aregenerative anemia receive blood at two to four-week intervals. It is apparent that in their treatment there are strong possibilities of the development of hemosiderosis and visceral fibrosis. Even with a conservative policy of prolonging the intervals between transfusions, the young patients inevitably receive massive injections of iron.

In consideration of possible pathologic reactions to these iron deposits, biochemical tests relating to hepatic and pancreatic function have been undertaken. Dr. John Ellis of the Department of Pathology has also been examining changes in available tissues from these patients. Up to the present sixteen children have been tested and reduced liver function has been observed in only one child, sixteen and a half years of age. Apparently functional integrity of this organ remains unimpaired for prolonged periods of iron accretion.

Another patient twenty years of age, referred to by Dr. Engle, developed diabetes in the last week of life and visceral lesions in the liver and pancreas, indistinguishable from endogenous hemochromatosis were present. That visceral fibrosis is related to age was further indicated in this patient by the fact that the quantity of iron present in the liver was substantially greater than that derived from transfusions. The studies by Dr. Ellis have emphasized not only that hemosiderosis in Cooley's anemia produced changes similar to hemochromatosis, but also demonstrated that the iron in the liver was derived from sources other than transfu-

sion. These observations therefore confirm previous reports of the increased absorption of iron in chronic anemias despite abundant tissue stores of this metal. The pathologic studies, together with the liver function studies, indicate that hepatic and pancreatic fibrosis develops slowly, becoming noticeable in the older individual. The effect of increasing age probably represents a temporal relationship, although an aberration of normal hormonal influence may also be involved.

THOMAS G. MORRIONE: We tried to approach the concept of storage protein in the liver as far as intercellular localization is concerned, utilizing differential centrifugalization. It seems as though Dr. Granick has nicely labelled storage protein, and I wonder whether he knows of any attempt at localizing intercellular distribution of ferritin, utilizing differential centrifugalization.

S. GRANICK: So far as I know, ferritin is soluble, so it would be rather difficult to localize ferritin by breaking the cell and trying to localize it.

WELLINGTON B. STEWART: To answer Dr. London's question regarding iron absorption in pernicious anemia: the determinations I cited were done under such circumstances that I think there can be but little question that the absorption was increased.

Dr. Graef and Dr. Smith have brought up many interesting points. I only wish to state that when considering diseases like thalassemia and sickle cell anemia one is adding many additional variables to the problem of siderosis. These people have genetically induced alterations in the metabolism of pigment and protein that perhaps profoundly influence the body's reaction to iron.

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EVENING LECTURE PROGRAM

MONDAY, OCTOBER 19

PRESIDENTIAL ADDRESS
ALEXANDER T. MARTIN

ERYTHROPOIESIS: NORMAL AND ABNORMAL
Ludwig Kast Lecture
WILLIAM B. CASTLE, Professor of Medicine, Harvard Medical School

IRON METABOLISM
S. GRANICK, Ph.D., Associate Member of the Rockefeller Institute

TUESDAY, OCTOBER 20

PRINCIPLES IN THE MANAGEMENT OF ANEMIAS
Carpenter Lecture
MAXWELL M. WINTROBE, Professor of Medicine, University of Utah College of Medicine

HEMOGLOBIN AND BILE PIGMENT METABOLISM
IRVING M. LONDON, Assistant Professor of Medicine, College of Physicians and Surgeons, Columbia University

WEDNESDAY, OCTOBER 21

THE HEMOLYTIC STATES
WILLIAM H. CROSBY, Lt. Col., MC, USA, Chief Department of Hematology, Army Medical Service Graduate School, Washington, D. C.

HEREDITARY ANEMIAS
R. JANET WATSON, Associate Professor of Medicine, State University of New York, College of Medicine at New York City

THURSDAY, OCTOBER 22

ANEMIAS IN INFANCY AND CHILDHOOD: DIAGNOSTIC AND THERAPEUTIC CONSIDERATIONS
CARL H. SMITH, Associate Professor of Clinical Pediatrics, Cornell University Medical College

BASIC MECHANISMS OF THE HEMOSTATIC PROCESS
MARIO STEFANINI, Associate Professor of Medicine, Tufts College Medical School

FRIDAY, OCTOBER 23

HEMOPHILIA
K. M. BRINKHOUS, Professor of Pathology, University of North Carolina School of Medicine

THE THROMBOCYTOPENIC PURPURAS
EUGENE L. LOZNER, Associate Professor of Medicine, State University of New York Upstate Medical Center, Syracuse

MONDAY, OCTOBER 26

WHITE BLOOD CELLS IN HEALTH AND DISEASE
CHARLES A. DOAN, Dean and Director of Medical Research, Ohio State University Health Center, Columbus, Ohio

POLYCYTHEMIA VERA: ITS COURSE AND TREATMENT
LOUIS R. WASSERMAN, Hematologist, The Mount Sinai Hospital, New York

TUESDAY, OCTOBER 27

LYMPHOMAS AND LEUKEMIA
Harlow Brooks Lecture
NATHAN ROSENTHAL, Consulting Hematologist, The Mount Sinai Hospital, New York

THE THERAPY OF LEUKEMIA
JOSEPH H. BURCHENAL, Professor of Medicine, Sloan-Kettering Division of Cornell University Medical College

WEDNESDAY, OCTOBER 28

HYPERSPLENISM
WILLIAM DAMESHEK, Professor of Clinical Medicine, Tufts College Medical School

CURRENT PROBLEMS IN BLOOD TRANSFUSION
PETER VOGEL, Director of the Blood Bank, The Mount Sinai Hospital, New York

THURSDAY, OCTOBER 29

FACTORS MODIFYING THE EFFECT OF RADIATION ON THE BLOOD AND BLOOD-FORMING TISSUE
LEON O. JACOBSON, Professor of Medicine, The University of Chicago

RETICULOENDOTHELIOSIS
PAUL KLEMPERER, Pathologist, The Mount Sinai Hospital, New York

FRIDAY, OCTOBER 30

CLINICAL IMPLICATIONS OF PLASMA FRACTIONATION
I. HERBERT SCHEINBERG, Associate in Medicine, Harvard Medical School

BLOOD VOLUME IN HEALTH AND DISEASE
SOLOMON A. BERSON, Assistant Director, Radioisotope Unit, Veterans Administration Hospital, Bronx, N. Y.

MORNING PANEL PROGRAM

11:00 A.M. at the Academy

Monday, October 19

NUTRITIONAL ANEMIAS.....*Chairman:* JOSEPH C. TURNER

Wednesday, October 21

METHODS IN HEMATOLOGY.....*Chairman:* DANIEL STATS

Friday, October 23

ERYTHROBLASTOSIS FETALIS.....*Chairman:* AARON KELLNER

Monday, October 26

THE ACTION OF DRUGS AND TOXIC AGENTS ON THE BLOOD PICTURE.....*Chairman:* PAUL REZNIKOFF

Wednesday, October 28

THERAPY OF LEUKEMIA.....*Chairman:* LLOYD F. CRAVER

Friday, October 30

THE PROBLEMS OF TRANSFUSIONS.....*Chairman:* PETER VOGEL

HOSPITAL CLINICS PROGRAM

CALENDAR OF CLINICS

All Clinics will be held from 2 to 5 P.M.

First Week

(*AT THE HOSPITALS*)

Monday, October 19	1.	Memorial *Hospital Representative:* LLOYD F. CRAVER
	2.	Flower-Fifth Avenue *Hospital Representative:* LINN J. BOYD
Tuesday, October 20	3.	Polyclinic *Hospital Representative:* JAMES P. CROCE
	4.	Lenox Hill *Hospital Representative:* CARL REICH
Wednesday, October 21	5.	St. Vincent's *Hospital Representative:* ANTONIO ROTTINO
	6.	Veterans Administration, Bronx *Hospital Representative:* JOSEPH GENNIS
Thursday, October 22	7.	Roosevelt *Hospital Representative:* R. STERLING MUELLER
	8.	St. Luke's *Hospital Representative:* LUIS A. AMILL
Friday, October 23	9.	Morrisania *Hospital Representative:* HERMAN L. FROSCH
	10.	Joint Diseases *Hospital Representative:* CARL REICH

Second Week

(*AT THE ACADEMY*)

Monday, October 26	11.	University *Hospital Representative:* EDWARD H. REISNER, JR.
	12.	Bellevue *Hospital Representative:* CHESTER H. WHITNEY
Tuesday, October 27	13.	Beth Israel *Hospital Representative:* LEON SUSSMAN
	14.	Presbyterian *Hospital Representative:* JOSEPH C. TURNER

Wednesday, October 28	15.	St. Clare's *Hospital Representative:* CARL REICH
	16.	New York *Hospital Representative:* RALPH L. ENGLE, JR.
Thursday, October 29	17.	Harlem *Hospital Representative:* NATHAN ROSENTHAL
	18.	Mt. Sinai *Hospital Representative:* LOUIS WASSERMAN
Friday, October 30	19.	Kings County, University Division *Hospital Representative:* R. JANET WATSON
	20.	Montefiore *Hospital Representative:* SAMUEL MELAMED

GRADUATE FORTNIGHT
REGISTRATION FEES — NON-FELLOWS

Fellows of The New York Academy of Medicine will be furnished registrations cards without application. A registration card will be sent to Non-Fellows upon receipt of check, payable to *The New York Academy of Medicine*, for $10.00 for the entire program, $5.00 for the *second week*.

Medical Officers of the Armed Services, in uniform, will be admitted without charge.

Interns and Residents will be admitted without charge, provided they present letters from their Chiefs of Service. They will be seated as facilities permit, after Fellows of the Academy and other registrants have been accommodated.

ANNOUNCEMENT

On Wednesday, October 21, 1953 at 5:00 P.M. The American Cancer Society, using the network facilities of the Columbia Broadcasting System, will initiate a series of television broadcasts in color which will be projected on the large 4½ by 6 foot screen. The programs, for physicians only and on a closed circuit, will originate at the Columbia-Presbyterian Medical Center and the Memorial Center. The broadcasts will be transmitted simultaneously to New York, Boston, Philadelphia, Pittsburgh, Toledo and Detroit. The New York receiver will be located at the **New York Academy of Medicine in Hosack Hall**. The Programs, which will emphasize the early diagnosis of cancer, will be broadcast on alternate Wednesdays to December 2, after which they will be presented weekly for a total of 30 programs.

MEDICAL RESEARCH FORUM

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This Forum is being arranged by the Committee on Medical Education of the Academy with the following stipulations:—

1. Presentations will be confined to *recent* original research in clinical medicine, surgery, or to research which is applicable to medicine or surgery in all clinical branches.

2. Presentations should be reports of work done within the last year or of progress in a continuing project. Previous submission to or presentation before a society will not prejudice the opportunity for presentation at the Forum.

3. In submitting application, the investigator is requested to state whether this work has been published, in toto or abstract, or has been submitted for publication; also, in cases where the investigator is working under the head of a department of a hospital or research institute, approval of the head of department is requested.

Presentations will be limited to twelve minutes. A period of free discussion will follow each presentation.

The publication of presentations is not a necessary condition but the Academy plans to publish promptly abstracts of presentations, if the author so desires. In order to expedite publication of abstracts, the Committee requests that the abstract submitted by the investigator be carefully prepared in the form in which publication is desired, with the understanding that publication of the abstract in the *Bulletin* of the Academy shall not preclude publication by the author in any other journal.

The Committee extends an invitation to all research workers of Greater New York to submit *an abstract of proposed presentation in QUADRUPLICATE*, not to exceed five hundred words in length, to the Secretary of the Committee on Medical Education of the Academy *during September and October 1953 and not later than November 1, 1953.* A formal invitation to participate in this program will then be extended by the Committee to the authors of papers selected for presentation.

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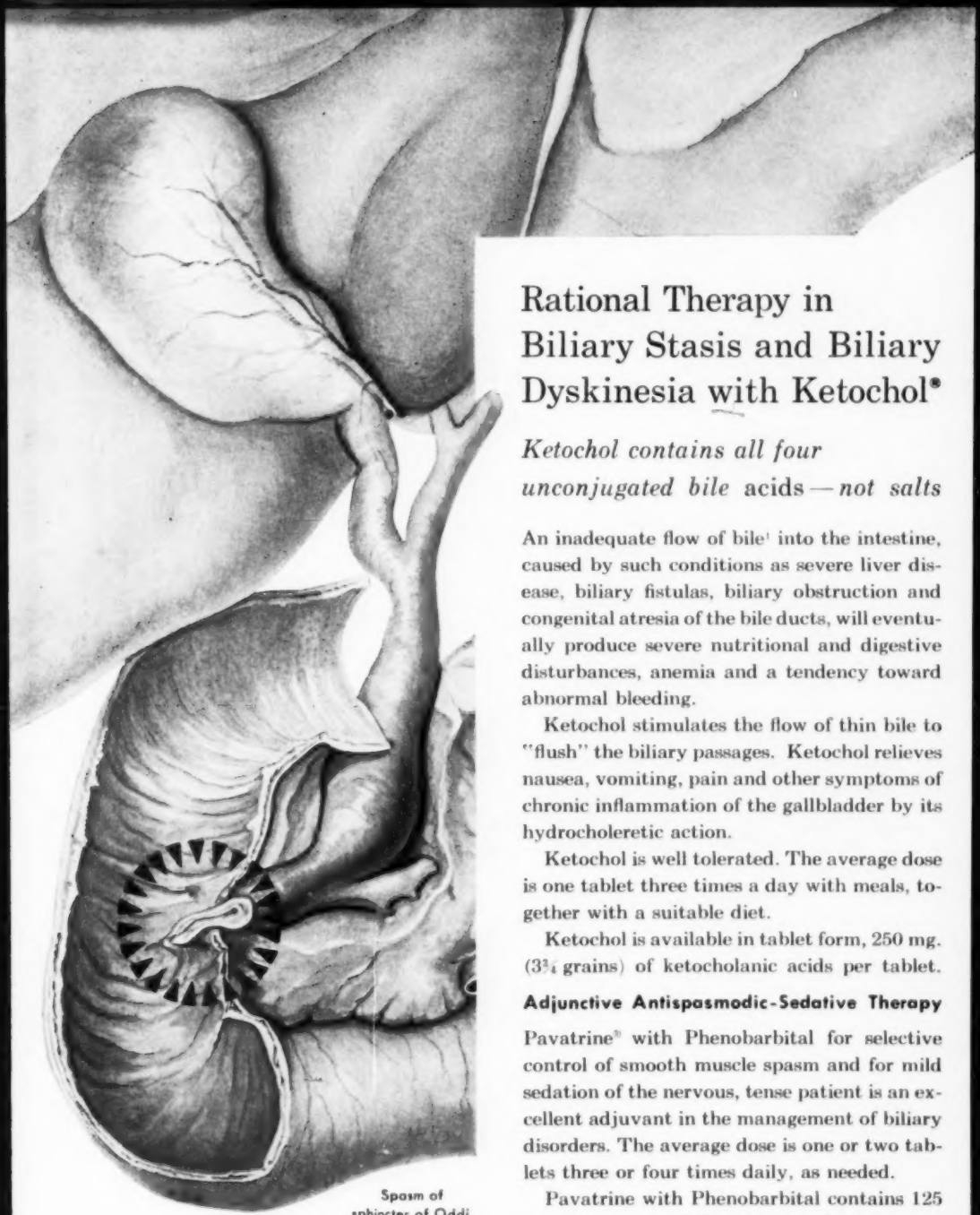
1. Behrman, H. T., Combes, F. C., Bobroff, A., Leviticus, R.: Ind. Med. & Surg. 18:512, 1949.
2. Turell, R.: New York St. J. M. 50:2282, 1950.
3. Heimer, C. B., Grayzel, H. G., and Kramer, B.: Archives Pediat. 68:382, 1951.



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1. Irvin, J. L.: The Secretion and Enterohepatic Circulation of Bile Acids: Replacement of Bile Acids in Biliary Insufficiency, North Carolina M. J. *13*:206 (April) 1952.

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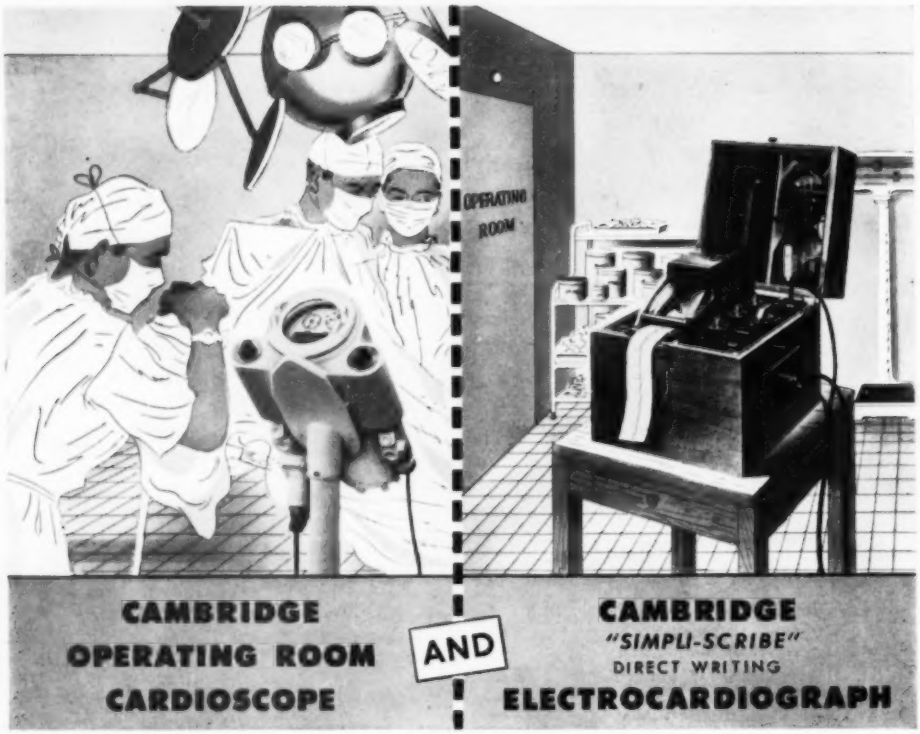

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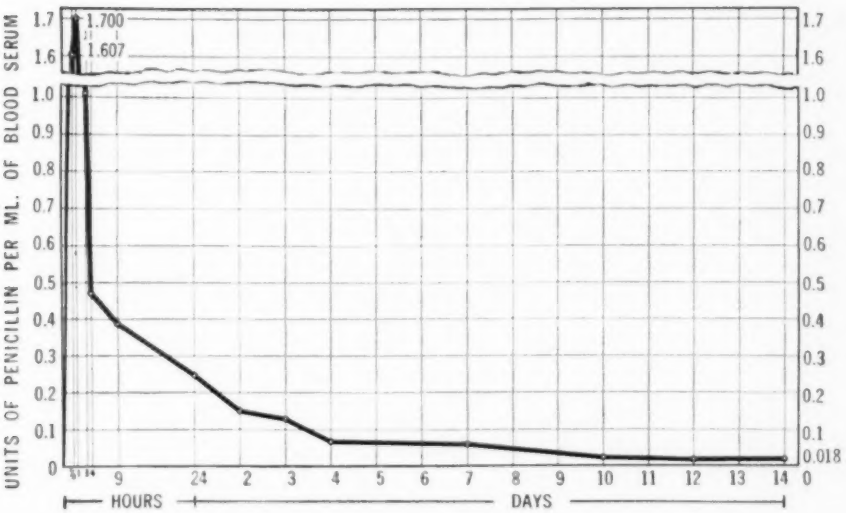

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1. Rogers, M. P., and Gray, C. L.: *Am. J. Digest. Dis.* 19:180, 1952.

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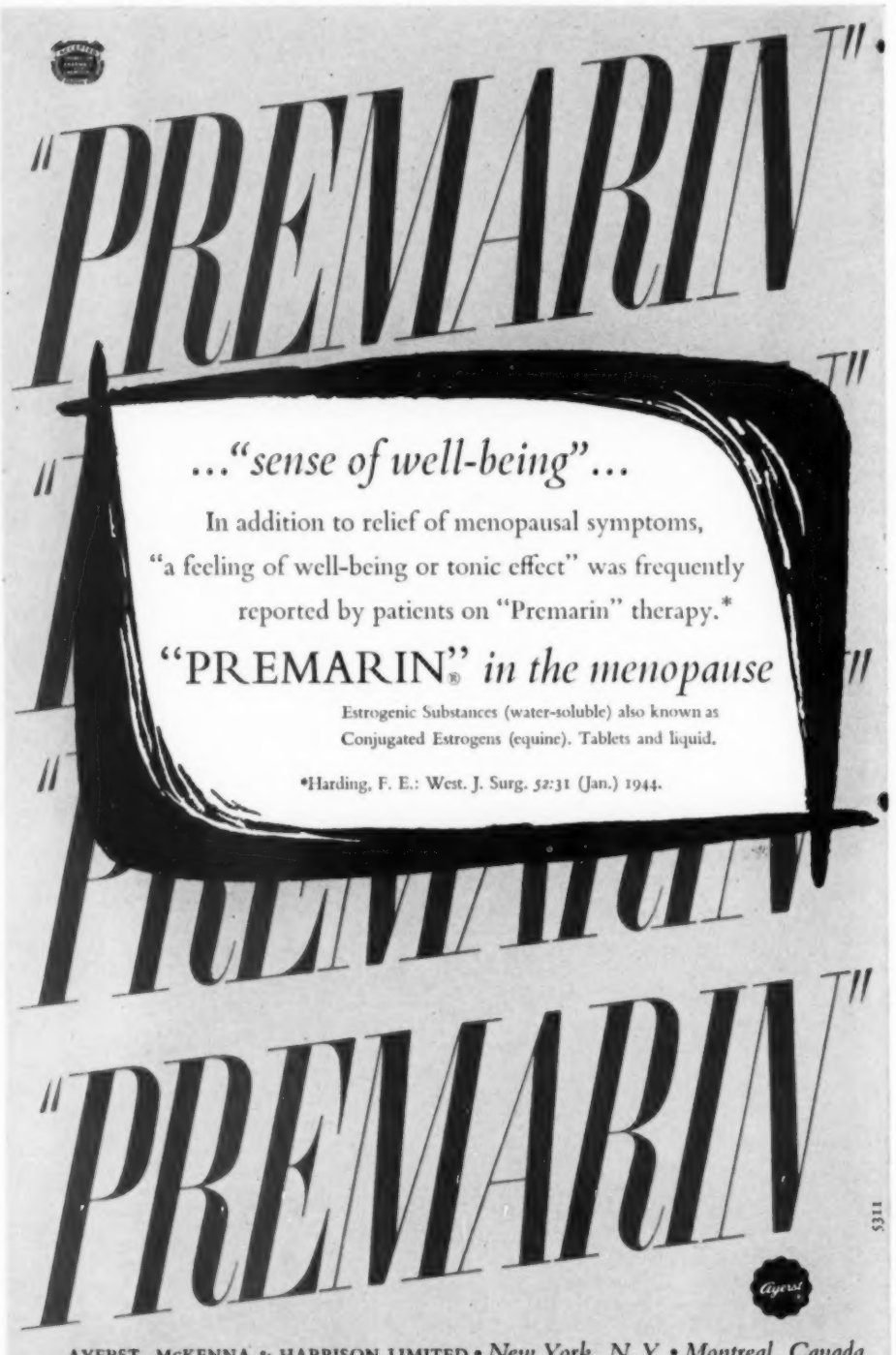
2. Fremont, R. E., and others: Postgrad. Med. 10:216, 1951.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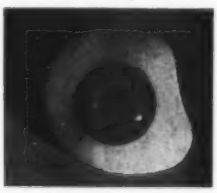

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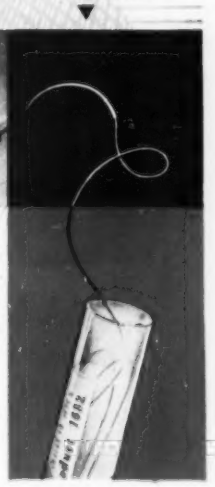

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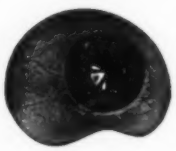

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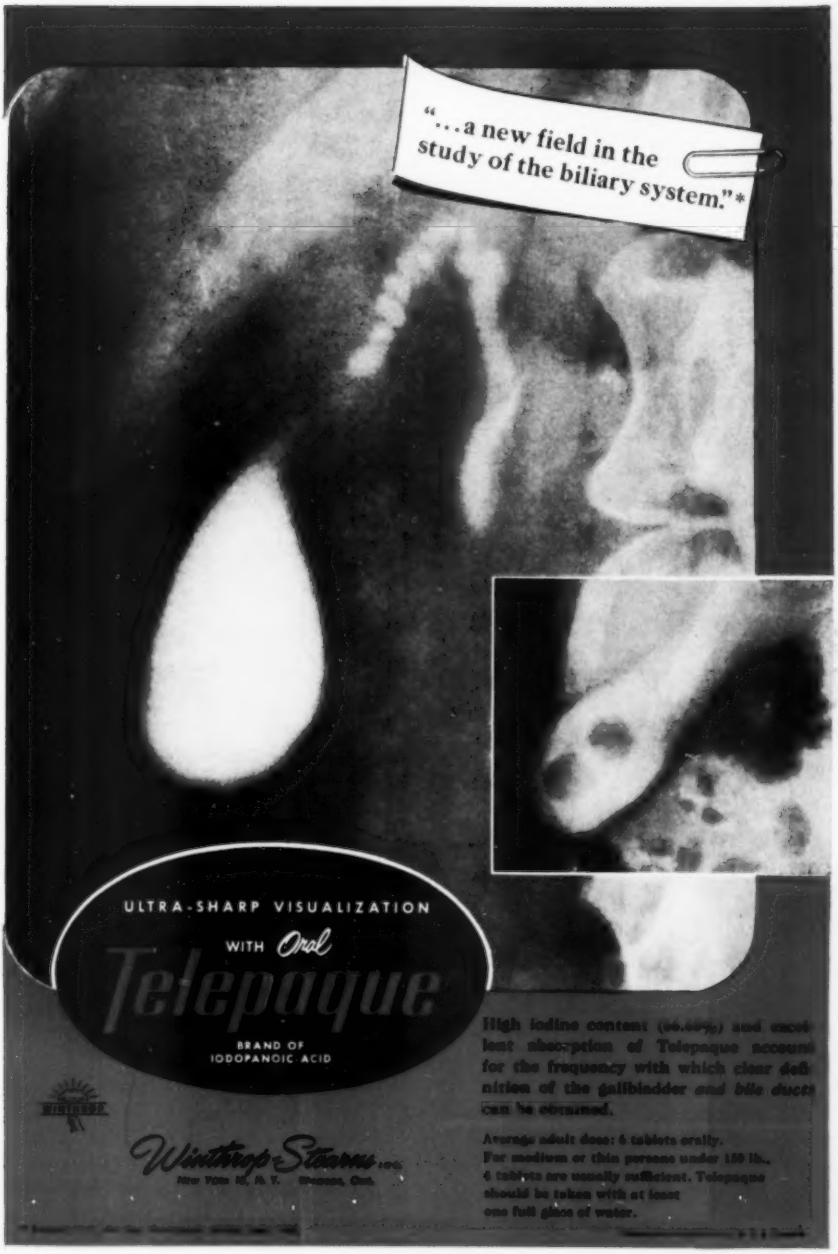
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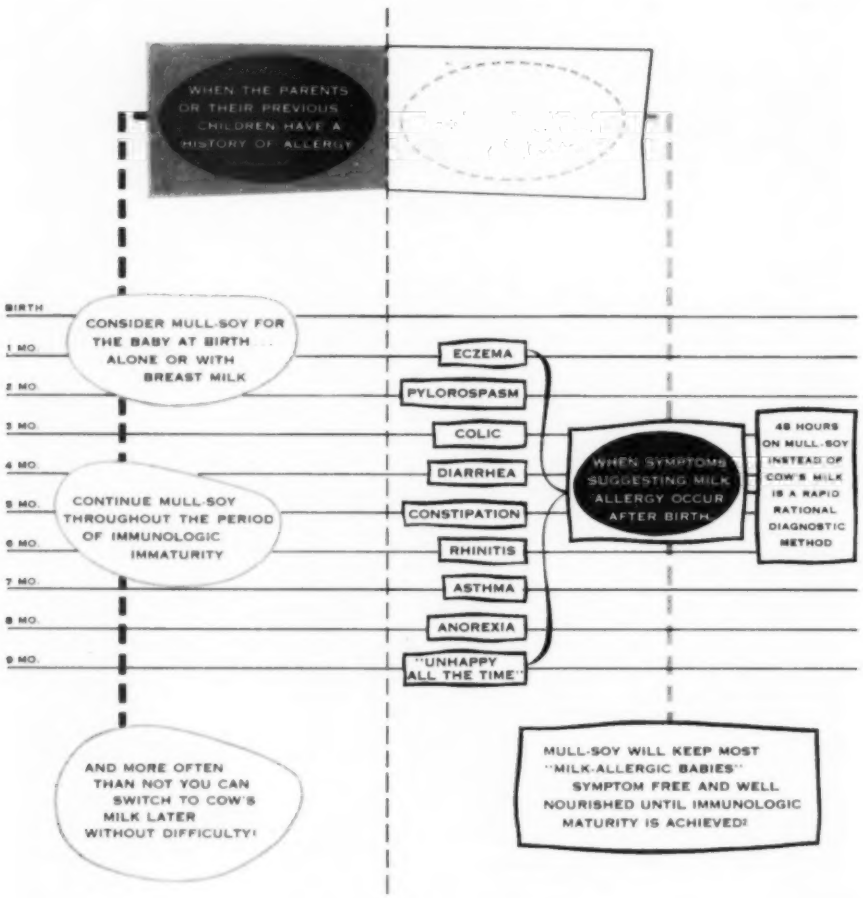
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1. Glaser, J., and Johnstone, D. E.: Ann. Allergy 10:433, 1952.
2. Clein, N. W.: Ann. Allergy 9:195, 1951.

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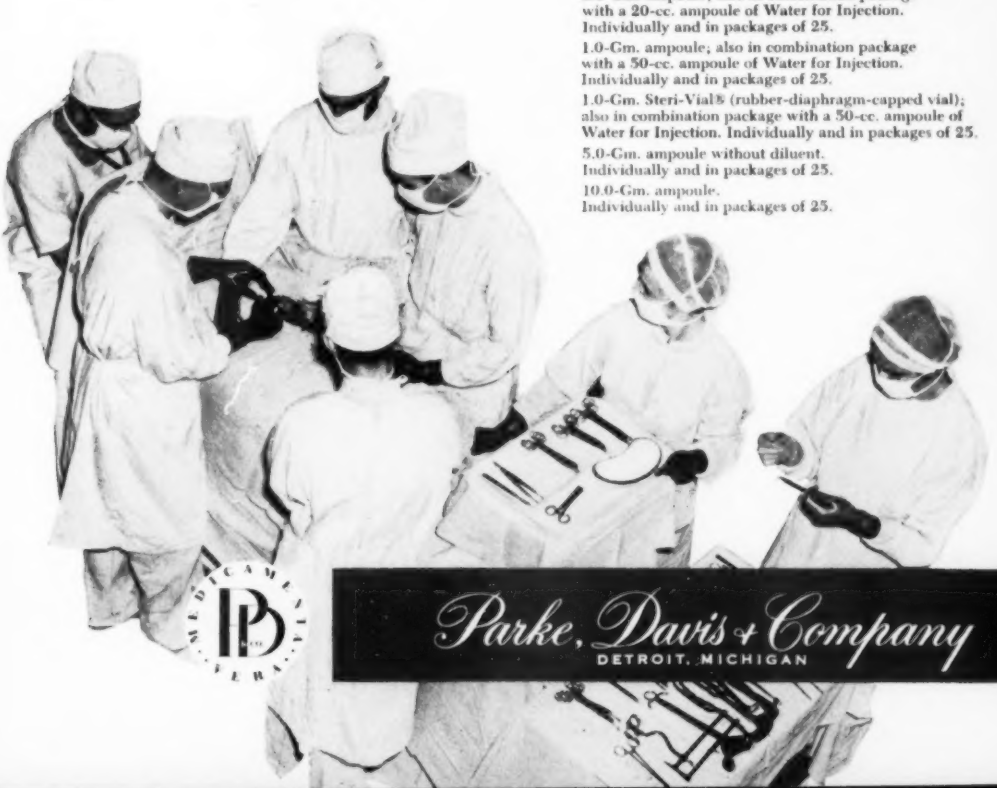

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*Stromme, W. B., and Rothnem, M. S. Clinical Experience with a New Gel-Alone Method of Contraception. World Population Problems and Birth Control. Ann. New York Acad. Sc. 54:831. May, 1952.

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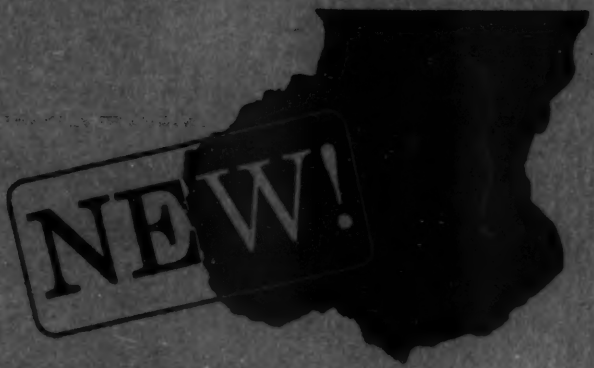

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